SYNTHESIS OF CHALCONE-BASED SIX AND SEVEN MEMBERED HETEROCYCLIC COMPOUNDS AND THEIR BIOLOGICAL ACTIVITIES AGAINST H1N1 VIRUS

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THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE
UNIVERSITY OF MALAYA
KUALA LUMPUR

2012

UNIVERSITI MALAYA

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Abstract

This thesis describes the synthesis of a library of chalcones and several flavanones and 1,5-benzothiazepines derived from chalcones and some biological studies of these compounds against neuraminidase (NA).

The environmentally benign one-pot method using PMA/SiO_2 in ethanol has successfully been applied toward the preparation of flavanone analogues from 2′-hydroxychalcones, 2′-aminochalcones and 2′-mercaptochalcones in reasonable yields. Reactions were screened in a variety of parameters, including solvents, temperatures, reaction time and amount of catalyst used. The nature of the solvent played a key role in the reaction where the reaction performed well in a polar protic solvent such as ethanol and only moderately in a polar aprotic solvent like acetonitrile. The reactions also seemed to be temperature dependent resulting a significant improvement in the yeild. All the reactions occurred smoothly in 1 mol% PMA-SiO_2 in ethanol. The reaction times varied from 8.5-22 hrs depending upon the type of chalcone.

Mono and dicationic ionic liquids (ILs) were employed as reusable catalysts for the synthesis of synthesize 1,5- benzothiazepines from chalcones and orthoaminothiophenol (*o*-ATP) in reasonable quantities. The counter ion was observed to influence the reaction time as well as yield of the reaction by effecting in the acidity of ILs. Better yields of 1,5- benzothiazepines were obtained in more acidic ILs.

Amongst all 1,5-benzothiazepines synthesized, 4-(4-methoxyphenyl)-2-(naphthalen-2-yl)2,3dihydrobenzo[b][1,4]thiazepine,MA12, was transformed to 3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine, 6MR during column purification.

The conversion of seven-membered ring, thiazepine to six-membered ring, thiazine is proposed to occure through a naphthyl shift or hydrogen shift.

The synthesized compounds (chalcones, flavanones and 1,5-benzothiaepines) were then investigated for their potency as NA inhibitors. Chalcones are shown to have some kind of activity as NA inhibitors. Quantitative structure-activity relationships for the chalcone compounds with the aid of 2D and 3D-QSAR models have been also studied. Flavanones and 1,5-benzothiazepines with promising Cdocker energy (compared to DANA with Cdocker interaction energy equal to -46.11 kcal/mol), were expected to be active against neuraminidase. However, the bioassay results were not corroborate with the modeling results. This observation presumably is due to the flavanones binding at the allosteric sites rather than the active site, the larger size of the seven-membered ring, lack of flexibility and solubility of 1,5-benzothiazepines.

342 words

Abstrak

Tesis ini menerangkan yang tentang sintesis beberapa chalcone dan flavanones serta 1,5-benzothiazepins dari chalcone dan kajian keaktifan biologi sebatian tersebut terhadap neuraminidase (NA).

Satu periuk kaedah mudah serta mesra alam menggunakan PMA/SiO_2 dalam etanol telah berjaya digunakan ke arah penyediaan analog flavanone daripada 2′-hydroxychalcones, 2′-aminochalcones dan 2′-mercaptochalcones dalam hasil yang munasabah. Tindak balas ini dilakukan dalam pelbagai parameter, termasuk pelarut, suhu, masa tindak balas dan mangkin yang digunakan. Sifat pelarut memainkan peranan penting dalam tindak balas di mana tindak balas menunjukkan prestasi yang baik dalam pelarut protic terkutub seperti etanol dan hanya sederhana di dalam aprotic terkutub pelarut seperti asetonitril. Tindak balas ini juga bergantung secara langsung kepada suhu di mana hasil turut meningkat dengan peningkatan suhu. Semua tindak balas berlaku dengan lancar pada 1 mol % PMA/ SiO_2 dalam etanol. Masa tindak balas berbeza dari 8.5-22 jam untuk penukaran pelbagai chalcone.

Cekar ionic (ILs) mono dan dikation bertindak sebagai mangkin yang boleh diguna semula untuk mensintesis 1,5-benzothiazepines dari chalcone dan orthoaminothiophenol (*o*-ATP) dalam kuatiti yang munasabah. Ion kaunter telah mempengaruhi masa tindak balas dan hasil tindak balas dengan mempengaruhi keasidan ILs. Hasil 1,5-benzothiaepines yang telah diperolehi dalam ILs yang lebih berasid.

Diantora 1,5-benzothiazepies disintesis, 4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepine, MA12, telah bertukar kepada 3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine, 6MR semasa proses pelunenon kromatografi. Penukaran gelang tujuh thiazepine ke gelang enam thiazine dijangkakan berlaku melalui peralihan naftil atau anjakan hidrogen.

Sebatian yang telah disintesis (chalcone, flavanone dan 1,5-benzothiazepines) telah dikaji potensinya bagai bahan perencat NA. Yang mana chalcones telah menunjukkan keaktifan terhadap NA. Hubungkait kuantitatif struktur- keaktifan untuk chalcone dengan bantuan model 2D dan 3D-QSAR telah juga dikaji. Flavanones dan 1,5-benzothiazepines dengan tenaga Cdocker yang baik (berbanding dengan DANA yang mampunyai tenaga interaksi Cdocker -46.11 kcal / mol), dijangka aktif terhadap neuramidase. Akan tetapi, keputusan bioasei tidak menyokong keputusan pemodelan. Ini mungkin disebabkan oleh flavanones yang terikat di laman allosterik berbanding tapak aktif dan saiz gelang tujuh yang besar serta, kekurangan fleksibiliti dan keterlarutan 1,5-benzothiazepines dalam pelarut yang digunakan.

Acknowledgements

This study would not have been possible without the help and assistance of many.

First and foremost, I would like to express my sincere gratitude to my supervisor, Professor Dr. Noorsaadah Abd. Rahman for her invaluable support and enthusiasm throughout the research project and the completion of this thesis. I gratefully acknowledge her for her constructive comments and suggestions on my research work. It has been a privilege for me to join the Drug design and development research group (DDDRG) and work under her supervision.

It is a pleasure to express my sincere gratitude to my co-supervisor, Professor Dr. Zanariah Abdullah for her supports and providing peaceful and pleasurable work atmosphere.

I appreciate Professor Dr. Habibah A.Wahab and Miss. Sairah Ikram from University Science Malaysia (USM) for helping me in bioassay. I am indebted to Professor Dr. Hossein Loghmani Khuzani from University of Isfahan, Iran, who gave me valuable scientific comments during his stay in Malaysia.

To the DDDRG group members with whom I have worked directly, I would like to collectively thank the group for providing helpful and critical discussions. I am especially proud to be one of them. In addition, I am truly grateful to my friends and

lab-mates, especially, Dr. Lee Yean Kee, Dr. Chee Chin Fei, Dr. Raghavendra Sakirollah, Dr. Vanajann Lee and Dr. Neni Frimayanti for providing helpful comments, guidance and encouragement.

Aside from the DDDRG group, I would like to thank my dear friends Miss. Shaghayegh Pezeshkpour and Dr. Hamid Khaledi for their moral supports, valuable comments and stimulating suggestions.

I would like to thank all the staff of the Department of Chemistry for their generous help, in particular, Miss. Norzalida Zakaria, Mr. Fateh Ngaliman, Mr. Jasmi Abd Aziz, and Mr. Siew Yau Foo for their help in NMR, LCMS analyses.

This work was made possible with the research grants from the University of Malaya (PS 200/2008A and PS363/2009B). I also truly appreciate the University of Malaya for Postgraduate fellowship award (PFA).

Lastly, I would like to thank my family for all their love and encouragement. My parents deserve special mention for their inspirable support and prayers. Pedar, in the first place was the person who put the fundamental of my learning character, showing me the joy of intellectual pursuit since I was a child. Maman, is the one who sincerely raised me with her caring and gently love.

My great and respectful parents' in-low, Pedar joon and Maman Fati, my lovely siblings and Marmar, thanks for being attentive and caring during these often very difficult times. My loving, supportive, encouraging, understanding and patient husband Alireza Jalali, whose faithful inspiring and love during this course is so appreciated.

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AcOH	Acetic acid
DANA	2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DMF	Dimethylformamide
EtOH	Ethanol
H1N1	Hemagglutinin neuraminidase
H_2SO_4	Sulfuric acid
H_3PO_4	Phosphoric acid
$H_3PMo_{12}O_{40}$	Phosphomolybdic acid
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
MeOH	Methanol
malonyl-CoA	Malonyl Coenzyme A
mp	Melting point
NaH	Sodium hydride

NaOH	Sodium hydroxide
NMR	Nuclear Magnetic Resonance
O-ATP	Orthoaminothiophenol
OAc	Acetate
OBz	Benzoate
OTf	Trifluoromethanesulfonate
O-PDA	Orthophenylendiamine
PEG	Polyethylen glycol
PMA/SiO_2	Phosphomolybdic acid supported on silica
PPh_3	Triphenylphosphine
rt	Room temperature
SAR	Structure-Activity Relationship
$TaBr_5$	Tantalum penta bromide
TEA	Triethylamine
TFA	Trifluroacetic Acid
THF	Tetrahydrofuran

CHAPTER 1

GENERAL INTRODUCTION

1.1 Introduction to Chalcones:

Chalcones are polyphenolic organic compounds belonging to a class of natural products called flavonoids. They are found in many different plant tissues like *Lauraceae* (Shimomura *et al*.1988), *Compositae* and *Leguminosae* (Xu *et al*. 2011) families. They are also known as pigments of the yellow to orange- colored flowers of many plant species such as *Coreopsis* and other *Asteraceae taxa* (Andersen *et al*. 2006). This group of natural products is abundant in vegetables and fruits. For example, significant amounts of chalcones like butein, phloretin, chalconargenin, arbutin and phloridzin occur in tomato, apples, pears, bearberry and strawberry (Nelson *et al.* 1993; Hijova *et al*. 2006)

Structurally, chalcones comprises two benzene rings, A and B, linked through an α, β-unsaturated carbonyl group (Figure 1.1).

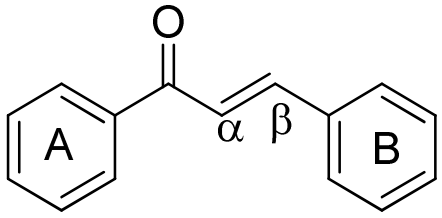


Figure 1.1 General structure of chalcone

The IUPAC name for the chalcone is 1, 3-diphenyl-2-propen-1-one. However, this nomenclature was thought to be too complicated for routine use. Therefore, semi-systematic names and trivial names are more commonly used (Andersen *et al*. 2006). As an example, 1-(2, 4-dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one is known as 2′, 4′, 4-trihydroxychalcone (semi systematic name) or (trivial name) isoliquiritigenin (Figure 1.2)

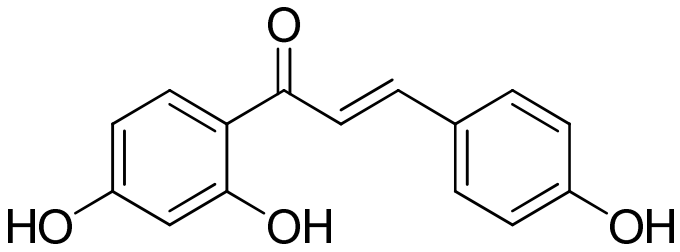
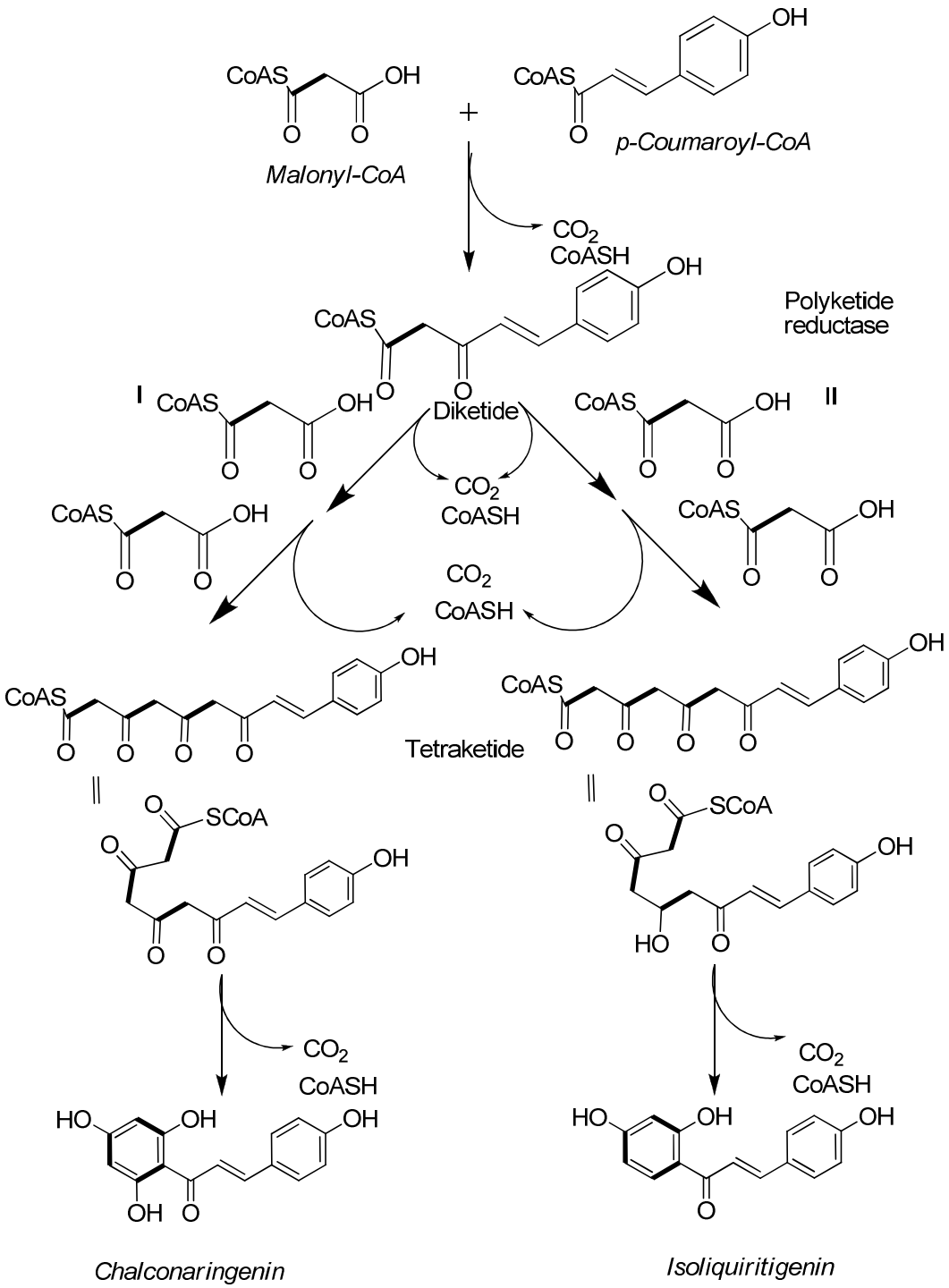


Figure 1.2 1-(2, 4-dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one

The biosynthetic pathway of *chalconaringenin* and *isoliquiritigenin* is outlined in Scheme 1.1. These chalcones are formed through condensation reactions of three molecules of malonyl coenzyme A (malonyl-CoA) with *p*-coumaroyl-CoA in the presence of chalcone synthase enzyme (Schroder et al. 1999). Malonyl-CoA (acetate pathway) and *p*-coumaroyl-CoA (shikimate pathway) are believed to be the origin of the ring A and B, respectively (Schroder et al. 1997).

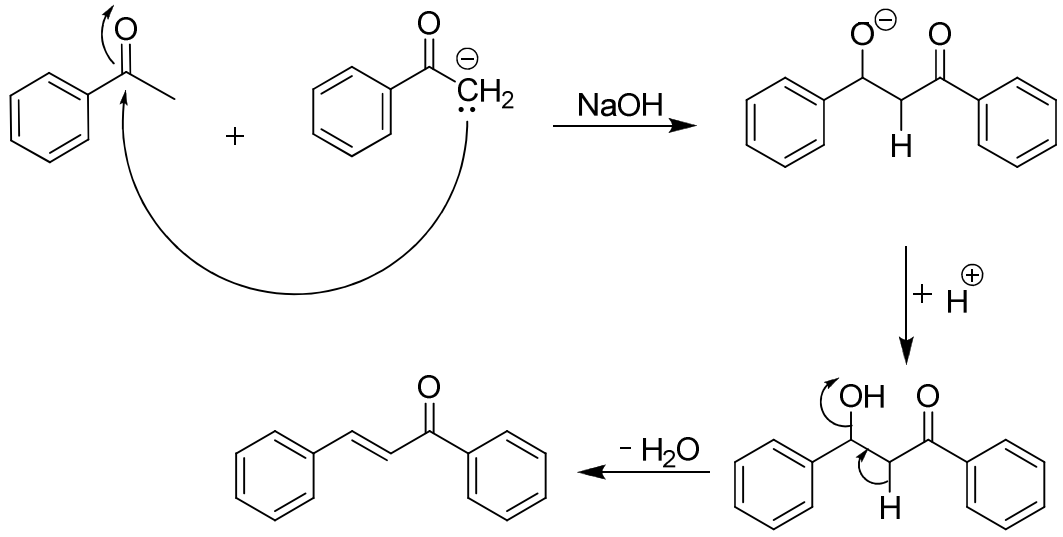


Scheme 1.1 Overview of the biosynthesis of (**I**) chalcones and (**II**)

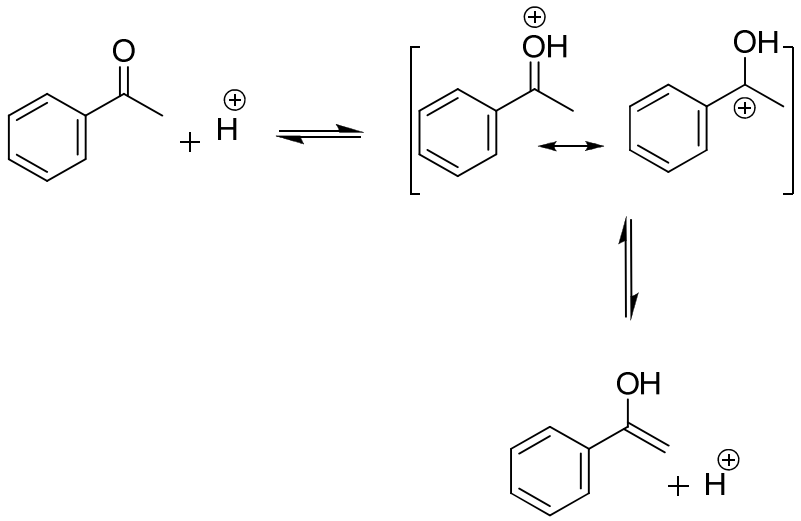
As shown in Scheme 1.2, the chalcones are often synthesized through an aldol condensation reaction between an acetophenone and a benzaldehyde in the presence of

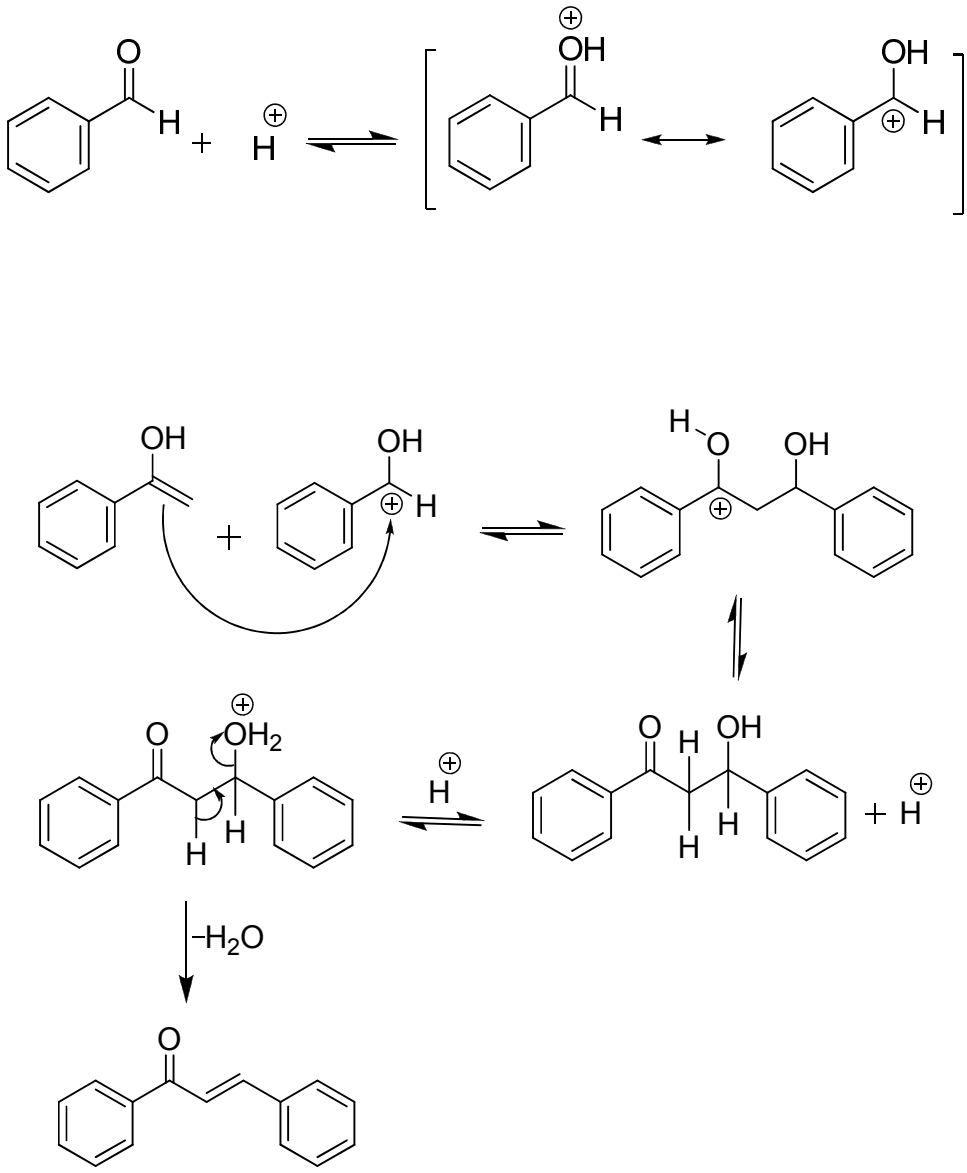
aqueous bases (**A**) or under acidic condition (**B**). Claisen-Schmidt condensation reaction is the most well-known method for the synthesis of chalcones (Patil *et al.* 2009).

A. Base catalyzed reaction:



B. Acid catalyzed reaction:





Scheme 1.2 General methods for the synthesis of chalcones

Chalcones are considered valuable pharmaceutical targets since they have been reported to possess a wide rang of biological activity such as anti-oxidant (Miller *et al*.1996), anti-inflammatory (Rojas *et al*. 2002), anti-microbial activities (Prasad *et al*. 2007). Structures of some reported bioactive chalcones is shown in Figure 1.3.

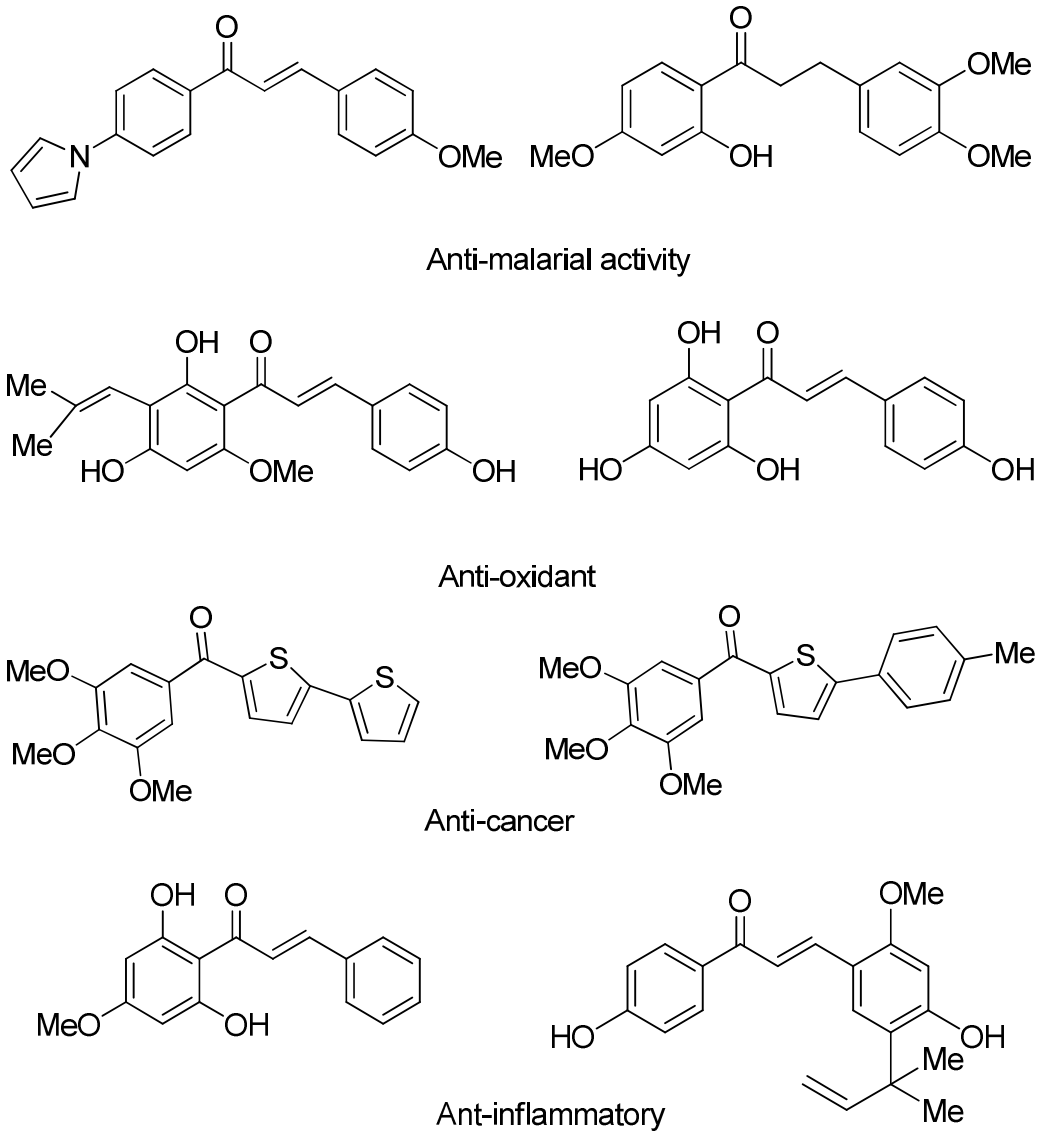
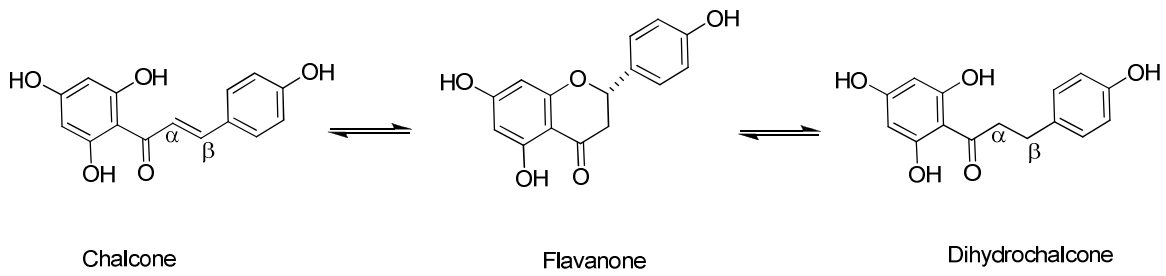


Figure 1.3 Structures of some biologically active chalcones

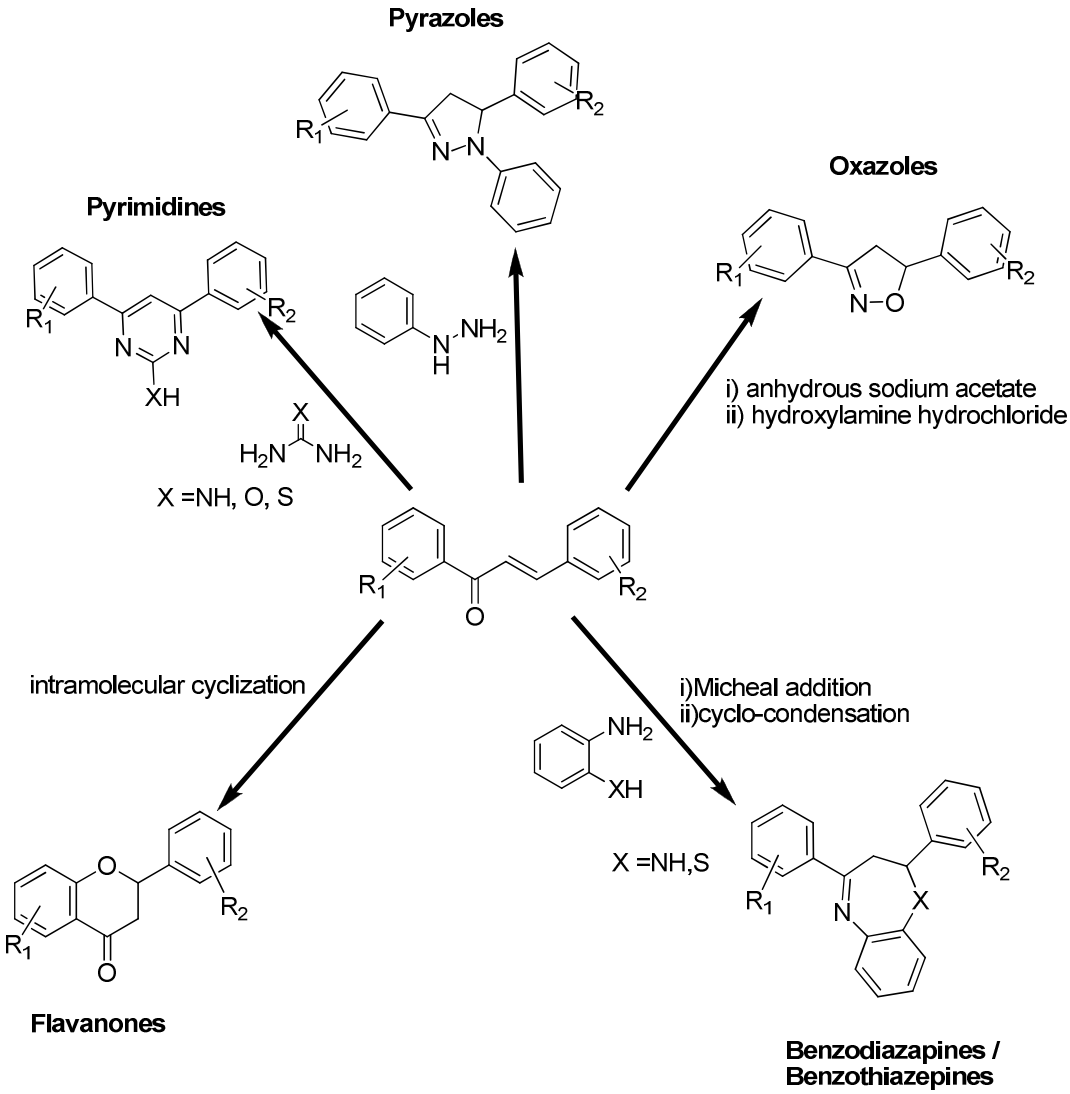
Interest in the chemistry of chalcone and chalcone derivatives intensified when it was discovered that they are promising precursors to other classes of flavonoids. As an example, in plants, open chain polyphenolic chalcones are transformed to flavanones and dihydrochalcones (Figure 1.4). The conversion of chalcones to flavanones in nature is often through a stereospecific reaction which is catalyzed by the enzyme chalcone isomerase. The co-occurrence of chalcones and flavanones as natural products could be explained by their close structural and biogenetic relationship (Andersen *et al*. 2006).



Chalcone Flavanone Dihydrochalcone

Figure 1.4 Conversion of chalcones to (2S)-flavanones and dihydrochalcones

Morever, as summarized in Scheme 1.3, this versatile class of organic compounds is considered as key building block for the synthesis of other biologically active compounds, like oxazoles, pyrazoles, pyrimidines (Bapna *et al*. 2008; Patil *et al.*2009), benzodiazepines (Du *et al*.2006) and benzothiazepines (Cherkupally *et al*. 2008). In this study, we focused on the synthesis of a library of chalcones. In addition, some of the chalcones synthesized have been used as a backbone to the synthesis of flavanones and 1, 5-benzothiazepines.



Scheme 1.3 Versatility of chalcones

1.2 Scope and objectives of this thesis:

Chalcones are considered as one of the most versatile naturally occurring organic compounds owing to their unique structure which enable them to act as a central core structure for constructing a variety of known bioactive heterocyclic five, six and seven-membered rings.

They have been shown to be promising moieties for drug discovery research over the past two decades. Although they are found to be widely distributed in plants, these sources are limited due to increasing population and the costly extraction and isolation process. Thus, synthesis can be considered as an alternative approach to provide these compounds with structural diversity and in larger quantities for further development. In this project, we aim to develop green, efficient and more effective synthetic routes to the bioactive compounds, comprising chalcones, flavanones and 1, 5-benzothiazepines. These three groups of compounds have been evaluated for the possible neuraminidase inhibitors by exploring computationaland bioassay techniques.

The present study has been conducted with the following objectives:

1. To develop an efficient one-pot synthesis of flavanone and its derivatives from hydroxyl, aza and thiochalcones.
2. To develop an efficient one-pot synthesis of 1, 5-benzothiazepines and its derivatives from chalcones
3. To assess activities of the synthesized compounds for inhibition of H1N1 virus.

This dissertation is consist of two main parts. Part **I** contain Chapters 2, 3, 4 and 5 give an overview of flavonoids and some of their biological properties. Chapter 2 is devoted to the discussion of the potential health benefits of flavonoids**.** Chapter 3 is a review of the most relevant synthetic routes for the synthesis of flavanone and its aza- and thio- analogues. The development of an efficient and green protocol for the synthesis of flavanones has been reported in Chapter 4. Chapter 5 deals with the synthesis of flavonoids analogues and their potential inhibition activity on H1N1 virus.

Part **II** contain Chapter 6, 7, 8 and 9 and deals with 1, 5-benzothiazepines and their bio importance.

Chapter 6 describes the biological properties of this class of heterocyclic rings. Chapter 7 is recap of some effective synthetic routes for the synthesis of 1, 5-benzothiazepines. The development of an efficient synthetic methodology reports in Chapter 8. Chapter 9 deals with the synthesis of 1, 5-benzothiazepines and their biological activity against H1N1 virus.

The products were characterized on the basis of spectroscopy data.

CHAPTER 2

FLAVONOIDS AND THEIR BIOLOGICAL IMPORTANCE

There have been considerable reports which suggested that vegetable and fruits consumption has a significant role in maintaining health and preventing chronic diseases such as heart disease and cancer (Joshipura *et al*.1999; Levi *et al* 1999 & 2000; Chen *et al*. 2002). This protective effect has been attributed to presence of the significant amounts of various types of flavonoids in such plant-based foods. For example, Peterson *et al*. have identified eight types of flavanones; namely, didymin, eriocitrin, hesperidin, naringin, narirutin, neoeriocitrin, neohesperidin, poncirin in citrus fruits such as grapefruit, lemons, and limes in a total amount of 17-27% (Peterson *et al*. 2006).

Flavonoids are class of polyphenolic natural products comprising two benzene rings (A and B) linked with a heterocyclic pyran ring C (Figure 2.1) (Harborne, 1994).

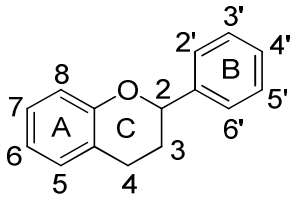


Figure 2.1 Basic flavonoid structures

Although more than 4000 unique species of flavonoids have been identified (Middleton *et al*. 2000), due to the ample range of bio- beneficial effects and the wide distribution, studies on the chemistry of flavonoid still remains attractive for many phytochemists and synthetic organic chemists.

Based on molecular structures, flavonoids can be divided into subclasses, *i.e.* chalcones, flavanones, flavones, isoflavones, , biflavones, flavonols, flavanonols, flavan-3-ols, anthocyanidins, aurones, coumarins, and catechins (Harborne, 1994; Pietta, 2000). In this project, focus is placed on the synthesis of chalcones and flavanones since the idea of extending nitrogen and sulfur substituted chalcones to the corresponding azaflavanone and thioflavanone is very attractive and it could provide useful information on the effect of these heteroatoms on their biological activities (Figure 2.2).

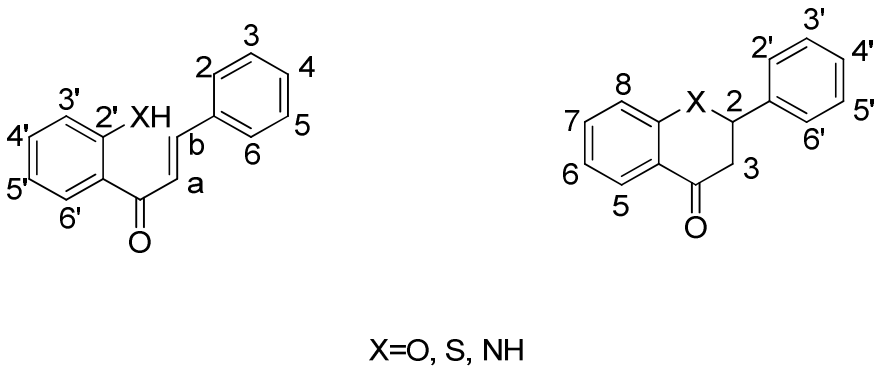


Figure 2.2 General structure of 2′-hydroxyl-,mercapto- and aminochalcones and corresponding flavanones

Flavonoids have been reported to possess a broad spectrum of biological activities such as anti-oxidant, anti-inflammatory, anti-cancer (Nijveldt *et al*. 2001; Pietta, 2000; Ballesteros *et al*. 1995; Heim *et al*.2002), anti-hypertensive (Wu *et al*.1992), anti-malarial (Li *et al*.1995), anti-bacterial (Schutz *et al*. 1995) anti-tumor (Xia *et al*.1998), anti-HIV(Ishikawa *et al*.1999) and radio protective agents (Blickenstaff *et al*. 1995). Some flavonoids have the ability to act as selective estrogen receptor modulators (Chen *et al*. 2004). Of the flavonoids, chalcones are one of the most versatile. These polyphenolic compounds contain two aromatic rings linked by an α, β-unsaturated carbonyl group. They are known to be precursors of isoflavonoids and other flavonoids such as flavanones. In addition, chalcones are considered to be the central core for other biologically active compounds like oxazoles, pyrazoles, pyrimidines (Patil *et al*. 2009) and azepines (Cherkupally *et al*. 2008). Besides its structural importance, chalcones are attractive species on their own due to their reported pharmaceutical properties such as anti-oxidant (Miller *et al*.1996), anti-inflammatory (Rojas *et al*. 2002), anti-microbial activities (Prasad *et al*. 2007).

Flavanones are one of the important subtypes of flavonoids, widely distributed in the plant kingdom. They found abundantly in plants of the family *leguminosae*, *compositae* and *moraceae* (Harborne, 1994; Harborne *et al*. 2001). Due to their unique rudimentary structure as starting material for many other bioactive compounds (Kumar *et al*.2008) there have been a growing interest for the synthesis and structure activity relationship studies on flavanones.

Azaflavanone derivatives had been reported to have good leads for non-steroidal anti-inflammatory drugs; NSAIDs (Philipp *et a*l.1980); while the thioflavanone derivatives have been used as precursors for biologically active compounds such as

benzothiazepine and thiochroman–4-one1, 1-dioxides (Holshouser *et al*. 1981). Nevertheless, limited number of studies had been carried out on the synthesis and SAR for nitrogen and sulfur containing flavanones especially in terms of their anti-viral activities. Therefore, in this study, we focused on synthesis and anti-viral inhibition properties of these compounds.

2.1 Neuraminidase inhibition effect:

The Orthomyxoviridaes are a family of RNA viruses, which includes five genera: Influenza virus A, Influenza virus B, Influenza virus C, Isa virus and Thogoto virus. Influenza virus A, B and C can cause influenza in birds, humans and some other mammals and amongst them, type A viruses are the most virulent human pathogens. Influenza A is further classified to subtypes like H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3 and H10N7. H and N stand from hemagglutinin (H) and neuraminidase (N) which are proteins on the surface of the influenza virus strain (Figure 2.3). Hemagglutinin is responsible for the binding of the virus to the host cells and causes agglutination of red blood cells. Neuraminidase is an enzyme which is in charge of the initiation of the influenza infection by promoting the release of the virus from the host cell.

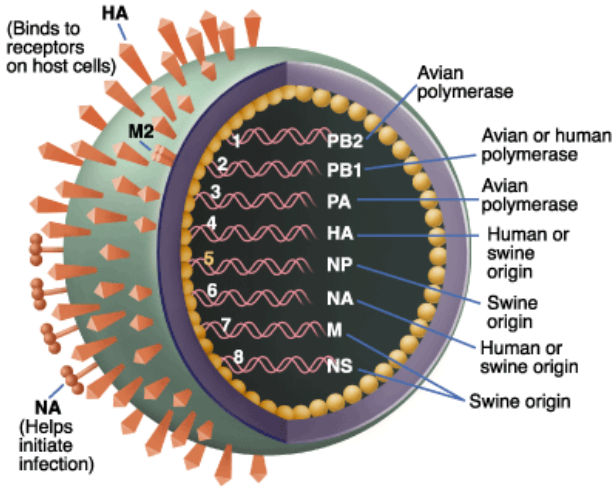


Figure 2.3 Structure of the influenza virion

Although there are different types of H and N proteins, the ones that normally cause influenza during flu seasons are H1N1 (swine and bird flu) and H3N2 (Hong Kong flu). The most common cause of human flu in 2009 (Pandemic H1N1/ 09 virus) was the swine origin subtype H1N1 virus which infected more than 1.6 million people with 19,633 death cases worldwide (Figure 2.4).The 2009 flu outbreak in Malaysia started in August 2009 with imported cases from affected countries like United States America and Australia followed by local transmission in June 2009 with 12,210 total number of infected cases and 92 death cases (Xinhua, 2009; *Bernama,* 2010*).* Although, yearly, influenza have been reported to caused numerous of mortality and morbidity and hospitalizations (Monto *et al*. 1997, Glezen *et al* .1982), but the worldwide outbreak of the new strain of the virus thet emerged in 2009 cause a global panic.

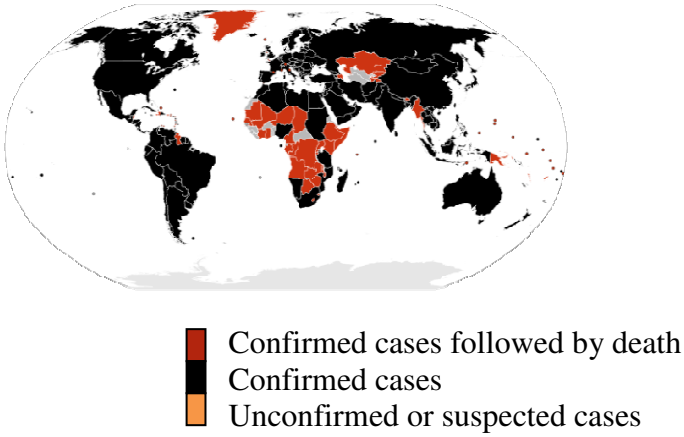


Figure 2.4 Map of infected countries in pandemic H1N1 2009

Until early twenty-first century, two methods were known to reduce the impact of influenza virus; vaccination and anti-viral drugs like rimantadine and amantadine. However, due to the ability of the virus to shift its surface antigenic proteins and rapid emergence of resistant viral strains, none of these methods could promote a complete protection or effectiveness against the influenza virus. Neuraminidase enzyme is an attractive target for many drug designers and medicinal chemists. This enzyme is a crucial part of influenza replication. Thus, finding suitable inhibitors to block the function of neuraminidase is possibly a more effective way to restrain or cure influenza (Babu *et al*. 2000).

Polyphenol rings, especially flavonoids are considered promising species for traditional herb based medicines. Ryu and co-workers investigated the neuraminidase inhibition activities of a series of isolated flavonoids from *Sophora flavescens* and found them to be fairly potent active with IC_{50} value of 20 µM or below in all cases (Ryu *et al*. 2008). In a similar study, a list of 25 flavonoids from various subtypes such as aurones, flavones and flavanones have been screened on influenza virus strains in which most of compounds exhibited moderate to good anti-influenza activity. In this study, A/PR/8/34

(H1N1), A/Jinan/15/90 (H3N2), and B/Jiangshu/10/2003 were used as the source of neuraminidase (Liu *et al*.2008). Isolated flavonoids from *Rhodiola rosea* and *Glycyrrhiza uralensis* roots also have been shown to have non-competitive inhibitory activity against neuraminidase (Jeong *et al*. 2009; Ryu *et al.* 2010).However, most of researches were conducted on naturally occurring flavonids and amongst all subtypes of flavooids, chalcones have not been extensively studied for their potency as NA inhibitors. Our recent interest in flavonoids, specially chalcones and flavanones has been inspired by the potential health benefits arising from the possible anti H1N1 activity of this class of compounds.

2.2 Anti-viral effects

A number of studies have been conducted on the anti-viral effect of flavonoids. *Calophyllum coumainins* and Baicalin have been reported to have anti-HIV-1 activity (Ishikawa *et al*.1999; Kitamura *et al*. 1998). Similarly, isolated flavonoids from *Geranium carolinianum L* have been shown to have reasonable anti-viral activity against hepatitis B virus (Li *et al*. 2008). Flavonoids like Glaranine and 7-O-methylglabranine were also reported to inhibit dengue viral growth (Sanchez *et al.* 2000). Tan *et al.* recently reported that panduratin A and its derivatives to exhibit good competitive inhibitory activities towards dengue 2 virus NS3 serine protease (Tan *et al.* 2006). In another study, Rajkumar and co-workers reported isolated flavonoids from *Poncirus trifoliate* such as Poncirin, rhoifolin, naringin and marmesin to be fairly effective mosquito repellent (Rajkumar *et al.* 2008).

2.3 Anti-oxidative effects

Oxygen metabolism is the most common reason for the production of reactive oxygen and free radicals in the human body which can cause cellular membrane damage, cell death and tissue damage. The presence of free radicals in the body eventually can result in many diseases and complications such as liver disease, cancer, asthma, and diabetes. Antioxidant agents have the ability to inhibit or delay the formation of free radical oxygen species by controlling the oxidation process of an oxidisable source. Flavonoids especially polyhydroxylated flavonols and catechins, can help the body counteract the effect of these free radical oxygen through various mechanisms like scavenging of the free radicals, quenching of the singlet oxygen by hydrogen donation and chelation of metal ions involved in free radical production (Patil *et al*. 2009, Miller *et al*.1996).

2.4 Anti-inflammatory effects

Inflammatory responses are often caused by the release of excess amount of different mediators by activated macrophages. For example, nitric oxide can cause edema, facilitate leukocyte movement in vessels and produce cytokine (Patil *et al*. 2009). Flavonoids like fluorinated chalcones are reported to prevent the nitric oxide generation from the nitric oxide synthase (Rojas *et al*. 2002). Release of arachidonic acid by other pro-inflammatory agents like cyclo-oxygenase (COX) and 5-lipoxygenase can be prevented by Quercetin (Boots *et al.* 2008; Loke *et al.* 2008; Valerio *et al.* 2009).

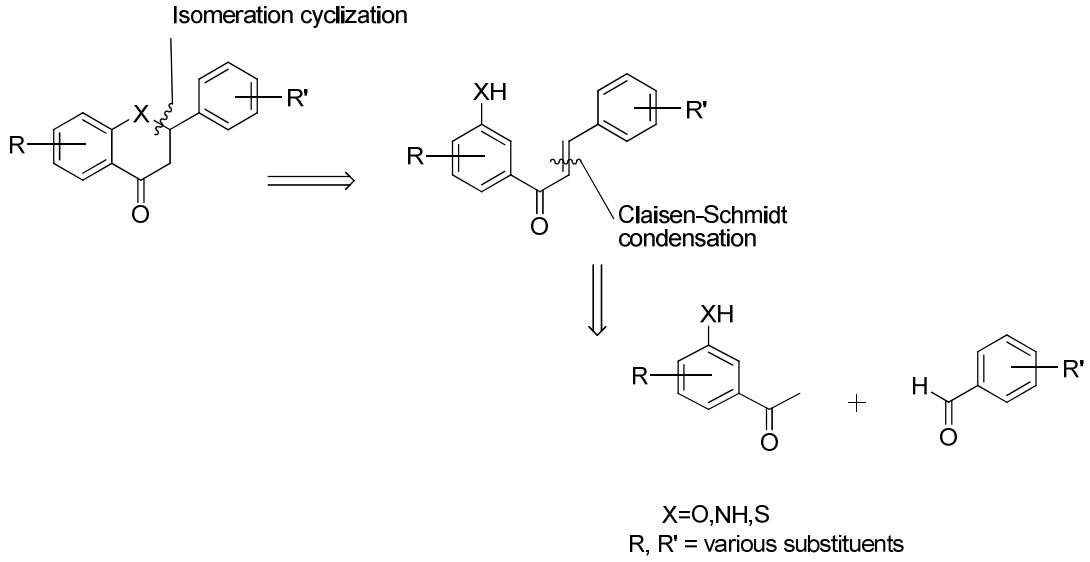
2.5 Anti-cancer effects

Flavonoids such as chromone and xanthone derivatives have been reported to be potent inhibitors for aromatase enzyme. Aromatase is the key enzyme involved in hormone-based breast cancer (Recanatini *et al*. 2001). Abyssinone II and its derivatives, a group of natural flavanones, were evaluated as aromatase inhibitors and have shown satisfactory inhibitory activity (Maiti *et al*. 2007). Substituted quinolones have shown cytotoxic and anti tubulin effects to various human tumor cell lines like lung carcinoma (A-549), breast cancer (MCF-7), renal cancer (CAKI-1), and melanoma cancer (SKMEL-2) *in vitro* (Xia *et al*. 1998). Thiochromones and thiochroman-4-ones were screened on CF1 male mice and successfully inhibit tumor growth (Holshouser *et al*.1981). In addition, it has been reported that flavonoids have antitumor activity to the human kidney carcinoma cells TK-10 *in vitro* (Cabrera *et al.* 2007).

CHAPTER 3

SYNTHETIC ROUTES TO THE FLAVANONES, AZAFLAVANONES AND THIOFLAVANONES

The synthesis of flavanones often involve an intramolecular conjugate addition of 2′-hydroxychalcone, 2′-aminochalcones and 2′-mercaptochalcones to the corresponding cyclic system in the presence of an acid or a base catalysts. The required chalcones normally synthesized *via* Claisen-Schmidt condensation of 2′-hydroxyacetophenone, 2′-aminoacetophenone and2′-mercaptoacetophenone with various benzaldehydes (Marais, 2005; Narender and Papi Reddy 2007). As outlined in Scheme 3.1, the retrosynthetic analysis consists of two primary disconnections, which can provide a facile and versatile synthetic route to produce a variety of products for the synthesis of flavanones without a lengthy protection-deprotection strategy.

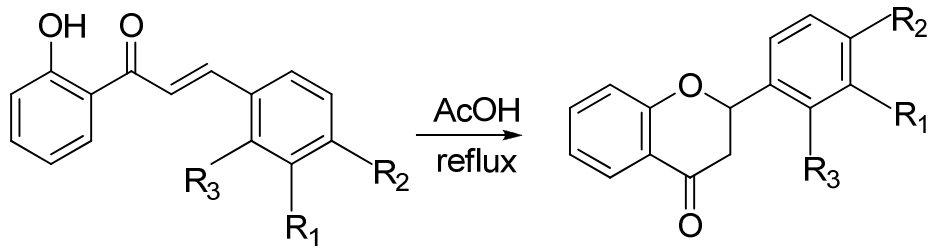


Scheme 3.1.Retrosynthesis strategy of flavanone synthesis

Acid catalyzed reactions can be performed using orthophosphoric acid, acetic acid (Cheng *et al.*1963) and silica gel (Sangwan *et al.*1984), while base catalysis has been carried out with strong alkali (Kaene *etal.*1970) and other bases such as L-proline (Chandrasekhar *et al*. 2005; Chandrasekhar *et al*. 2007) . Other cyclization methods involve different reaction conditions such as light (Stermitz *et al.*1975) heat (Harris *et al.*1967), electrolysis (Sanicanin *et al.*1986) and Ni/Zn/K halide catalysis (Ali *et al*. 1984).

3.1 Acetic acid catalyzed flavanone synthesis

Acetic acid is one of the most common solvents / acid catalysts in organic synthesis due to its commercial availability and reasonable price. It is reported to be a promising catalyst for the transformation of 2′-hydroxychalcones to the corresponding flavanones. As shown in Scheme 3.2, cyclization to produce flavanone was carried out by refluxing the 2′-hydroxychalcone (1equivalent) in 25ml of glacial AcOH for 72h. The reaction mixture was poured into water and extracted with organic solvents. The organic layer was dried and purified by column chromatography to yield the corresponding flavanone in moderate to good quantity (Cabrera *et al*.2007).



R_1= H, R_2= H, R_3= H

R_1= H, R_2= Br, R_3= H

R_1= H, R_2= H, R_3= Br

R_1= H, R_2= OBn, R_3= H

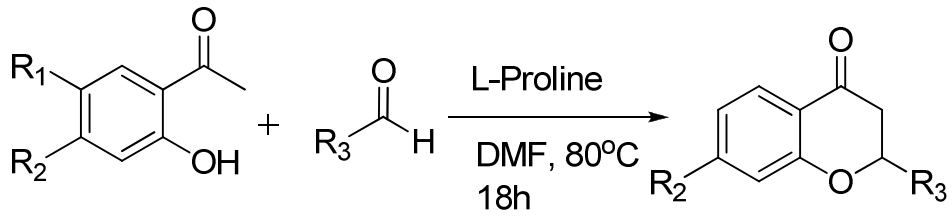
R_1= H, R_2= OMe, R_3= H

R_1= H, R_2= OCH_2O, R_3= H

Scheme 3.2. Synthesis of flavanones using AcOH

3.2 L-proline catalyzed flavanone synthesis

An efficient method reported by Chandrasekhar *et al*, involved a reaction of variety of aryl aldehydes with substituted 2′-hydroxyacetophenones in the presence of 30mol% L-proline in DMF (Scheme 3.3). In a typical experiment, 2′-hydroxyacetophenone and benzaldehyde were heated together with 30mol% L-proline in DMF (0.02M) for about eighteen hours. Ether extraction followed by water wash gave the crude which was purified by column chromatography to furnish flavanone and chalcone in a ratio of 7:3. (Chandrasekhar *et al*. 2005).



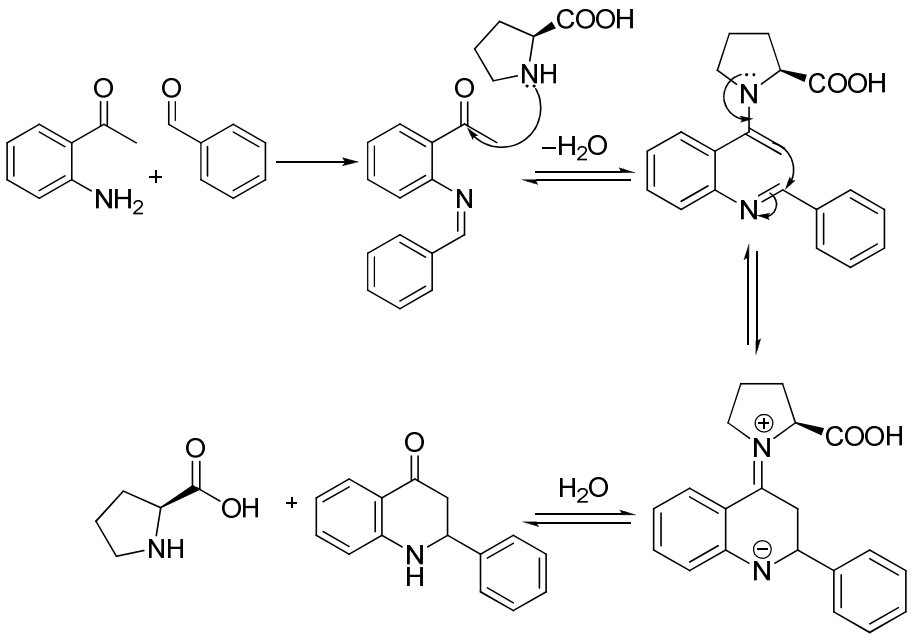
R_1=H, CH_3, OCH_3

R_2=H, Cl

R_3=ph, *p*-NO_2 ph, *p*-OCH_3 ph

Scheme3.3. S.Chandrasekhar synthetic route of flavanone

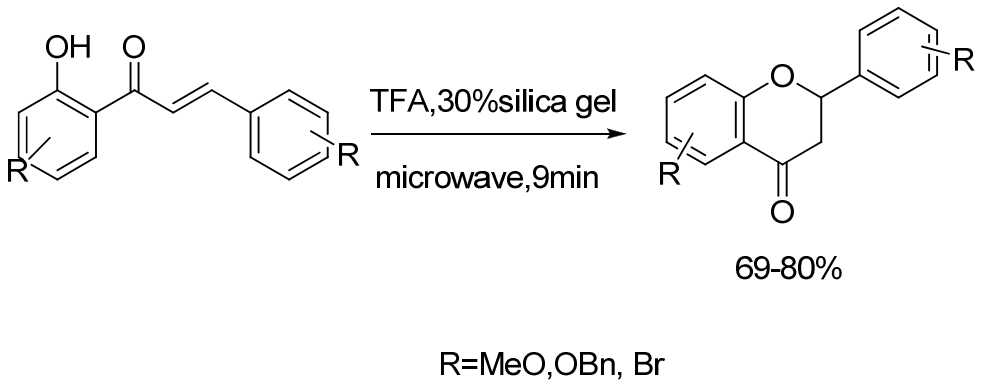
A similar method has been employed by Chandrasekhar by replacing 2′-aminoacetophenone with 2′-hydroxyacetophenone in the synthesis of azaflavanones (Chandrasekhar *et al*. 2007). In this approach 2′-aminoacetophenone and benzaldehydes were stirred with 30mol% of L-proline in methanol (5ml). The reaction proceeded smoothly at room temperature for 48h. As shown in proposed mechanism by Chanasekhar *et al*, unlike other previous approaches, benzaldehyde and 2′-aminoacetophenone underwent a Schiff-base reaction followed by addition of nitrogen from L-proline to the carbonyl group and cyclization reaction to form the desired azaflavanones.(Scheme 3.4)



Scheme3.4 Proposed mechanism for the synthesis of Azaflavanone using L-poline

3.3 Microwave accelerated solvent-free synthesis of flavanones

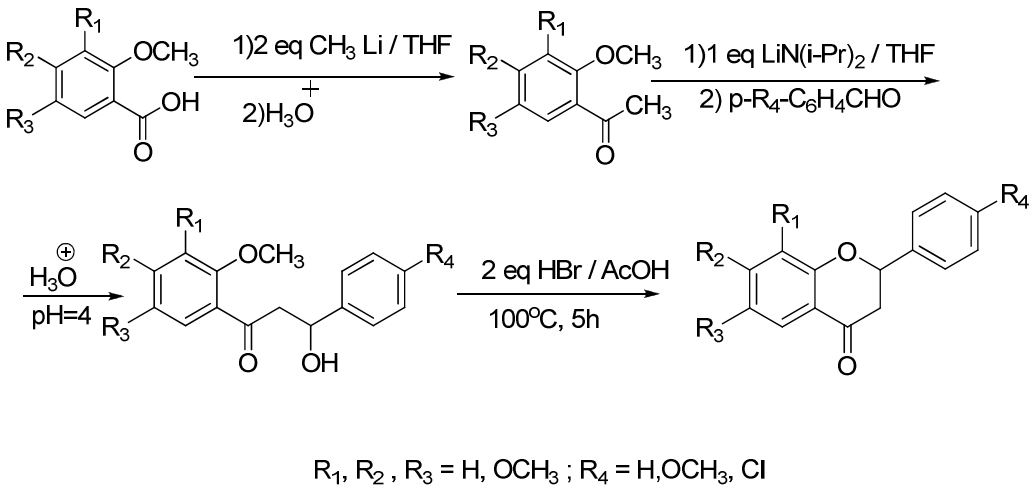
In this method, the synthesis of flavanone was carried out by using organic acid (TFA) and a mineral support (silica gel) in the microwave. The main objective of this method is to minimize the usage of conventional solvent for the flavanone synthesis. 0.2ml TFA and 1g silica gel was added to the mixture of 0.1mmol chalcone in 5ml dry DCM. The solvent was then evaporated under vacuum, and the resulting powder was irradiated by microwave. The crude was extracted with ethyl acetate and washed with water and purified by column chromatography (Sagrera *et al* .2003). The reaction is summarized in Scheme 3.5



Scheme 3.5. Microwave Accelerated Solvent-Free Synthesis of Flavanone

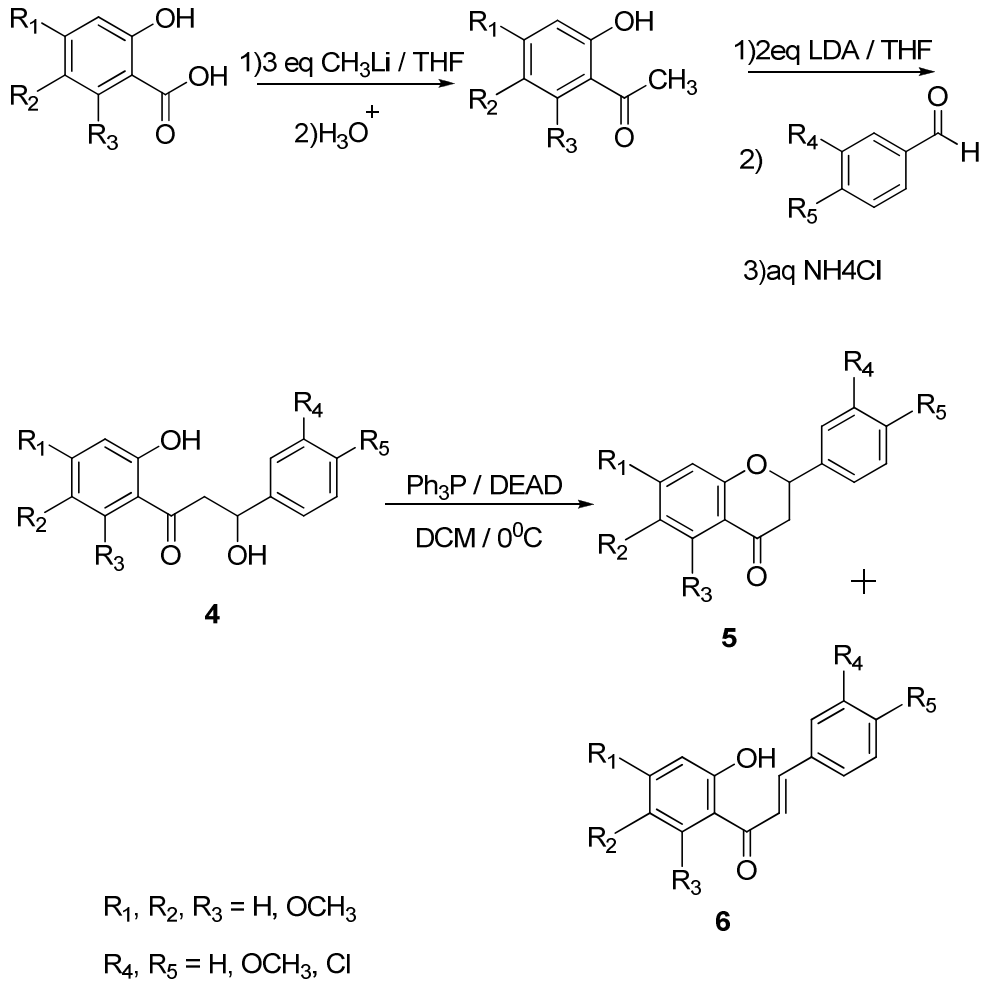
3.4 Jea In Lee synthetic method

Unlike most of the synthetic routes which proceed through intramolecular cyclocondensation of 2′-hydroxychalcones to the corresponding flavanones; Lee and co-workers introduced a method where the reactions proceeded without involving in 2'-methoxy or 2'-hydroxychalcones. 2′-Methoxy benzoic acid was treated with 2 equivalents methyllithium in THF to produce 2'-methoxyacetophenone which subsequently treated with 1 equivalent LDA in THF at -20^{o}C to yield the corresponding lithium enolate. Addition of benzaldehyde to this reaction mixture followed by acidification (pH=4) and extraction produced 1-(2'-methoxyphenyl)-1-oxo-propan-3-(4'-chlorophenyl)-3-ol as a key intermediate. The desired flavanones were obtained by heating of this intermediate with 2 equivalents 48% hydrogen bromide in glacial acetic acid. The reaction is summarized in Scheme 3.6 (Lee *et al.* 2004).



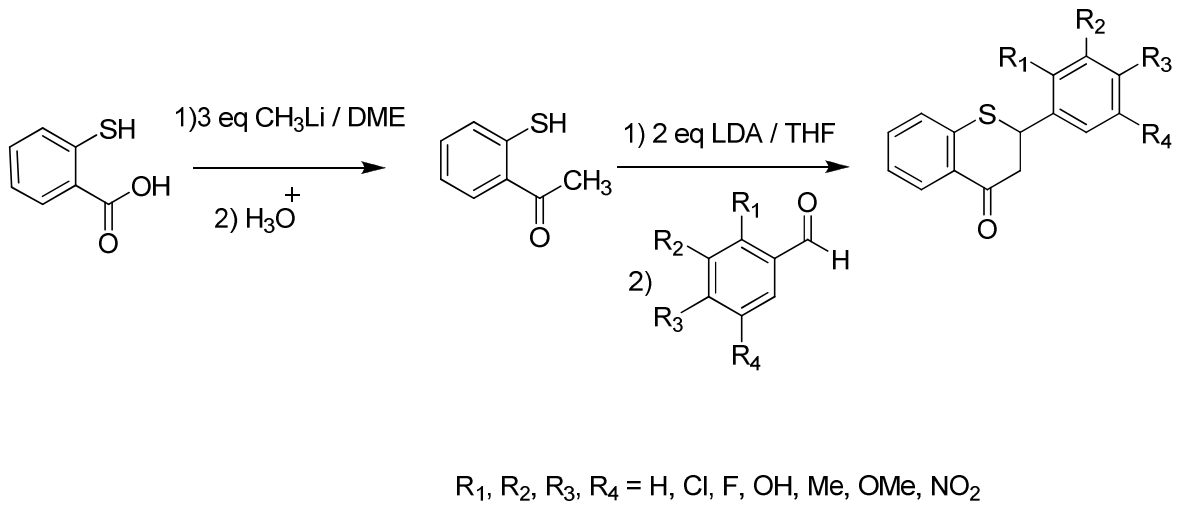
Scheme 3.6. Synthesis of flavanones using 2′-Methoxy benzoic acid.

In another approach, Lee and co-workers repeated the procedure by treating 2′-hydroxybenzoic acids with 3 equivalents methyllithium in THF to yield the corresponding 2′-hydroxyacetophenones which was then reacted with benzaldehydes in the presence of 2 equivalents LDA in THF at -78^{o}C for about 1hr. The mixture was quenched with saturated NH_4Cl solution to give 1-(2'-Hydroxyphenyl)-1-oxo-propan-3-phenyl-3-ols (4, Scheme 3.7). The residue subsequently underwent cyclodehydration reaction following slow addition of Ph_3P/diethylazodicarboxylate (DEAD) in dichloromethane at 0^{o}C to yield the desired flavanone (5) and 2′-hydroxychalcone (6) in a ratio of 13:1 (Lee *et al.* 2007).



Scheme 3.7. Synthesis of flavanones using 2′-hydroxy benzoic acid.

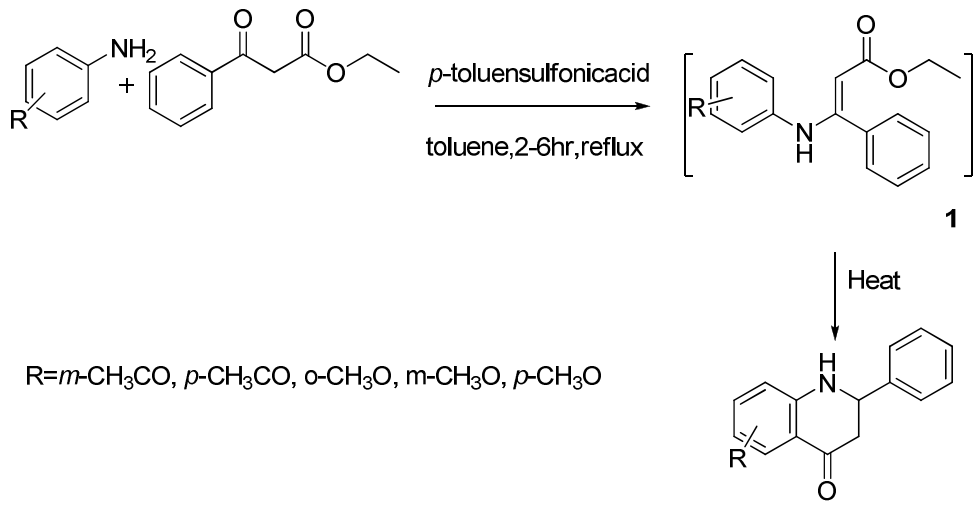
Similar methodology by Lee and co-workers was employed for the synthesis of thioflavanone by methylation of thiosalicylic acid (Scheme 3.8). The resulting mercaptoacetophenone was treated with LDA in THF at -15^{0}C. To the reaction mixture, a solution of benzaldehydes in THF was added. After 2hrs of stirring, the mixture was quenched with 0.5 N-HCl and extracted with methylene chloride followed by aqueous sodium bicarbonate workup and column chromatography purification gave thioflavanones as the product (Lee *et al.*2008).



Scheme3.8. Synthesis of thioflavanones from thiosalicylic acid

3.5 Synthesis of azaflavanones from substituted aniline

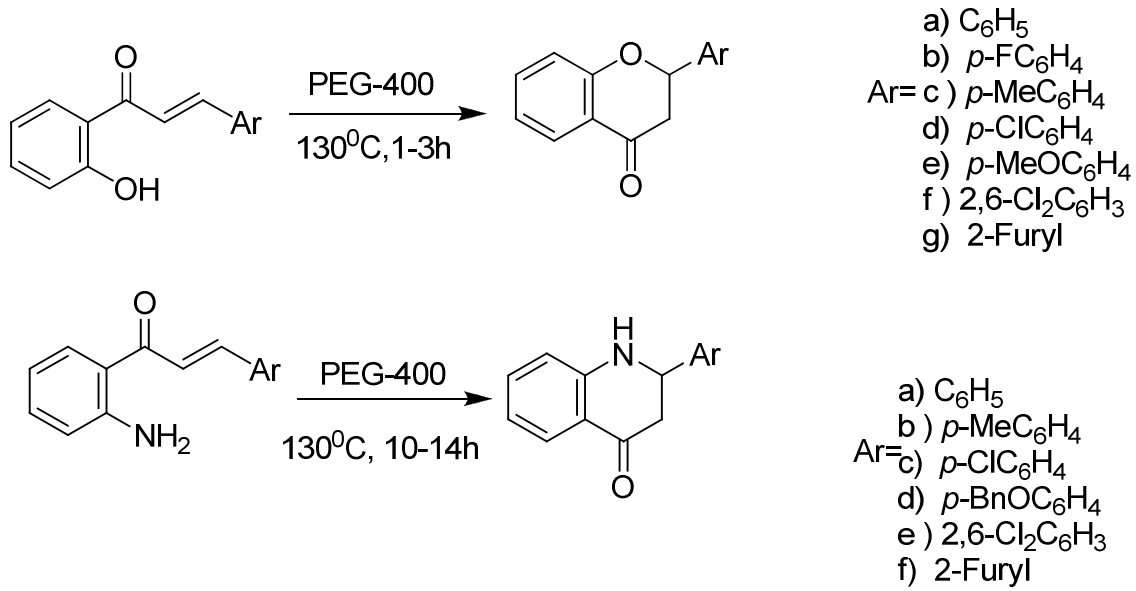
As summarized in Scheme 3.9, in this method, a mixture of substituted aniline, ethyl benzyl acetate and *p*-toluenesulfonic acid were refluxed in toluene to give the intermediate 1 which subsequently cyclized under thermal condition to yield the azaflavanones in reasonable yield (Park *et al*.2004).



Scheme 3.9 Synthesis of azaflavanone using *p*-toluenesulfonic acid

3.6 Eco-friendly polyethylene glycol promoted flavanone synthesis

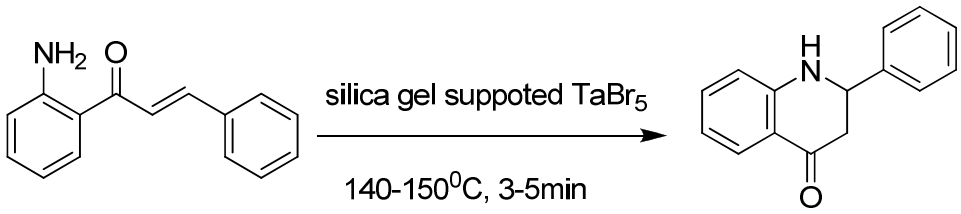
Kumar and co-workers employed an eco-friendly method to synthesize flavanones and azaflavanones by reacting 1.4 mmol 2′-hydroxychalcones or 2′-aminochalcones in 0.5 ml solution of polyethylene glycol (PEG-400) at optimized temperature (130^{o}C) for appropriated time (Scheme 3.10). The reaction mixture was extracted with diethyl ether and washed with brine. Removal of solvent and column chromatographic purification yielded the corresponding flavanones and azaflavanones in reasonable yields (Kumar *et al*.2008).



Scheme 3.10. Synthesis of flavanones and azaflavanones in PEG-400

3.7 Synthesis of azaflavanone using Silica gel supported $TaBr_5$

This method is based upon heat-facilitated intramolecular Michael addition of amino group in 2′-aminochalcones to an α, β-unsaturated ketone using silica supported tantalumpentabromide as catalyst (Scheme 3.11). Even though the reactants were heated relatively high temperatures (140-150^{0}C) in the absence of solvent; the configuration of both the $TaBr_5$ catalyst and the 2′-aminochalcones is secured due to the attachment of substrate and catalyst to the silica gel matrix. In this method, a solution of 1mmol 2′-aminochalcones in 1-1.5ml DCM was added to$TaBr_5$ (5–10 mol %). 200mg Oven dried silica gel added to the mixture, DCM was then evaporated and the mixture was heated up to140-150^{o}C with stirring. After completion of the reaction, the mixture was extracted with diethyl ether and purified by column chromatography. The same reaction condition for the synthesis of flavanone from 2′-hydroxychalcones has been carried out but the isomerization reaction of 2′-hydroxychalcones to corresponding flavanone was not as efficient as of 2′-aminochalcones to azaflavanones (Ahmed *et al*. 2006)

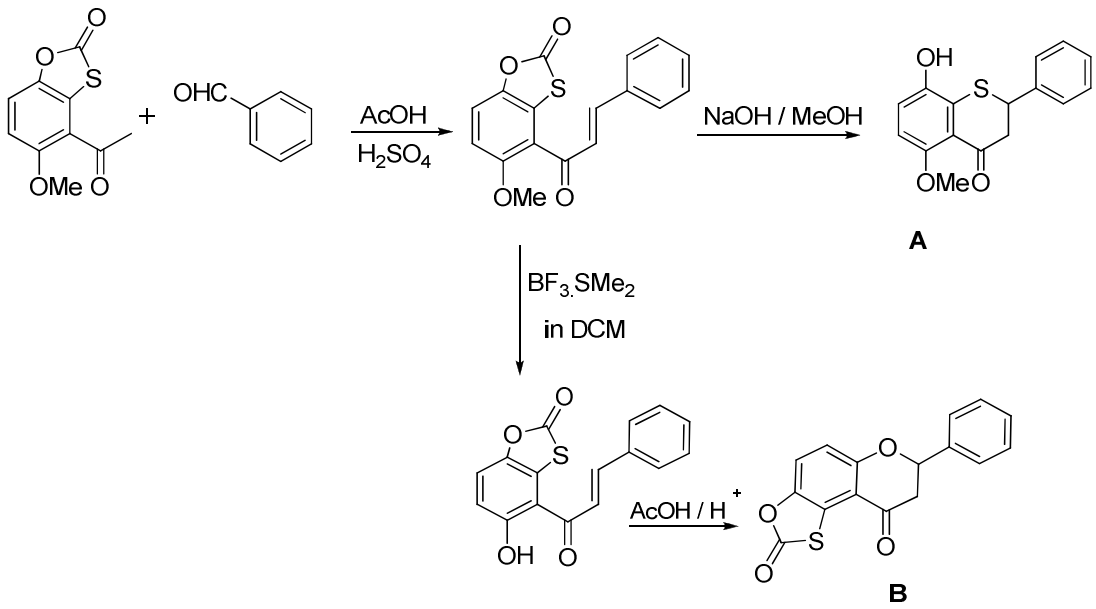


Scheme 3.11. Azaflavanone synthesis using silica gel supported tantalumpentabromide

3.8 Synthesis of thioflavanone and flavanones from oxathiolone chalcones

Thioflavanones have been synthesized from specific oxathiolone chalcones. In the first step, chalcones bearing oxathiolone ring were synthesized through a reaction of the corresponding acetophenone and benzaldehyde (1:1.5 mmol) in acetic acid (1.3mmol) and catalytic amount of concentrated sulfuric acid (Konieczny *et al*.2007). Due to the base sensitivity of oxathiolone ring, base catalyzed Claisen-Schmidt reaction is not applicable to the synthesis of these types of chalcones. Indeed, the chalcones then underwent cyclization reaction by refluxing the corresponding chalcones in basified methanol followed by acidification of the reaction mixture with hydrochloric acid (Schem 3.12, A)

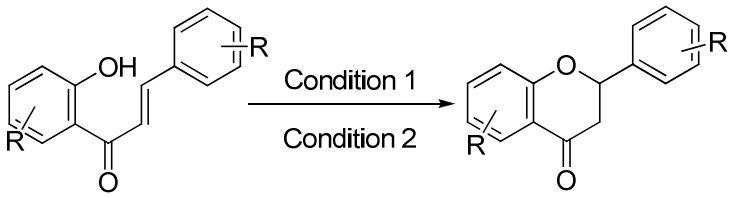
For the synthesis of flavanones from oxathiolone- chalcones to occur, presence of a methoxy group at 5^{th} position of oxathiolone- chalcones is necessary (Scheme 3.12, B). Treatment of the chalcone with $BF_3.SMe_2$ in DCM followed by quenching with water resulted in the hydroxychalcones which upon stirring in acetic acid containing catalytic amount of sulfuric acid to give oxathioloflavanone (Konieczny *et al*. 2009).



Scheme 3.12. Synthesis of thioflavanone and flavanones from oxathiolone chalcones

3.9 Flavanone synthesis catalyzed by anhydrous potassium carbonate

Mondal and co-workers refluxed a mixture 1mmole of 2'-hydroxychalcones and anhydrous potassium carbonate (1.5gr) in dry acetone for 3-5hrs to give flavanones. The same reaction was repeated in a microwave by adding 1.5 gram anhydrous potassium carbonate to a solution of 2'-hydroxychalcones (1mmol) in DCM (Scheme 3.13). Removal of the solvent followed by irradiation of the resulting solid in microwave for 3 minute at 131^{o}C gave flavanone in good yield (Mondal *et al*. 2011).



Condition 1 : anhydrous K_2CO_3, reflux in dry aceton for 3-5 hrs

Condition 2 : anhydrous K_2CO_3, microwave irradiation for 3 min.

Scheme 3.13. Synthesis of flavanones using anhydrous potassium carbonate

However, many of the reported methods suffer from disadvantages such as low yields, long reaction times, strong acidic medium leading to environmental pollution, high cost of the catalyst and lack of recovery and reusability of the catalysts. In addition, most of the reported synthetic methodologies are not applicable to synthesis of all subtypes of flavanones. Hence, there is still a need to develop mild, high-yielding protocols for the

cyclization of substituted chalcones to flavanones via environmentally friendly methods. Nowadays, heterogeneous catalysts are preferred over homogeneous processes due to their regenerability and reusability, ease of handling and simplicity of work up. Considering the bio-importance of flavanones, exploring a green alternative in flavanone synthesis motivated us to carry out a study on heterogeneous condition alternatives.

Heteropoly acids (HPAs) are a group of solid acids with bifunctional catalytic ability in homogeneous and heterogeneous conditions (Kozhevnikov *et al*.1998*).* They have been used as efficient catalyst in various organic reactions such as the Fries rearrangement of phenyl acetate (Kozhevnikova *et al*.2002), Friedel-Crafts acylation of phenols (Kaur *et al.*2002), oxidation of alcohols (Firouzabadi *et al*. 2003), Nazarov rearrangement (Murugan *et al*. 2010). Phosphomolybdic acid belongs to the family of heteropoly acids (HPAs) and has gained importance as a catalyst since it is inexpensive, environmentally friendly and stable at high temperature (*Kumar* et al*.2005*; Kozhevnikov *et al*.1998). It has been used as catalyst in many chemical transformations such as: regioselective opening of aziridines with nucleophiles (Kumar *et al*. 2004), chemoselective hydrolysis of acetonides (Yadav *et al*.2005), Ferrier rearrangement (Yadav *et al*.2006), selective deprotection of *tert*-butyldimethylsilylether (Kumar *et al*. 2005), and aziridination of olefins with chloramine–T (Kumar *et al*. 2004). The structure of phosphomolybdic acid is shown in

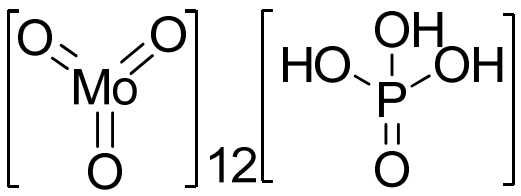


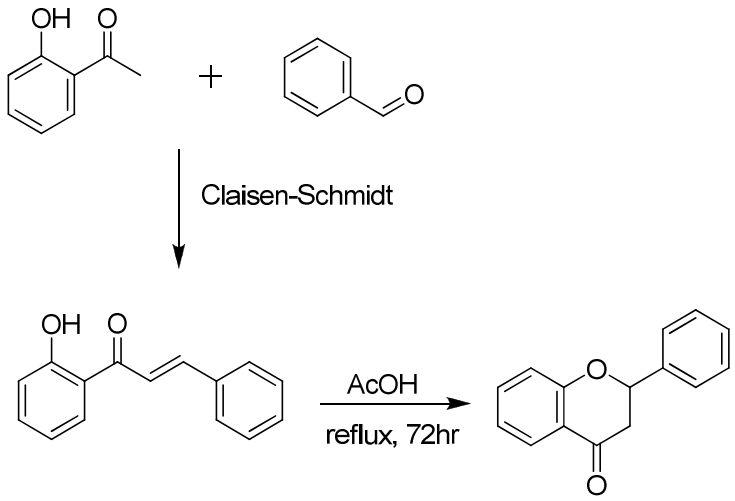
Figure 3.1 Structure of phosphomolybdic acid.

CHAPTER 4

A GREEN APPROACH TO FLAVANONE SYNTHESIS

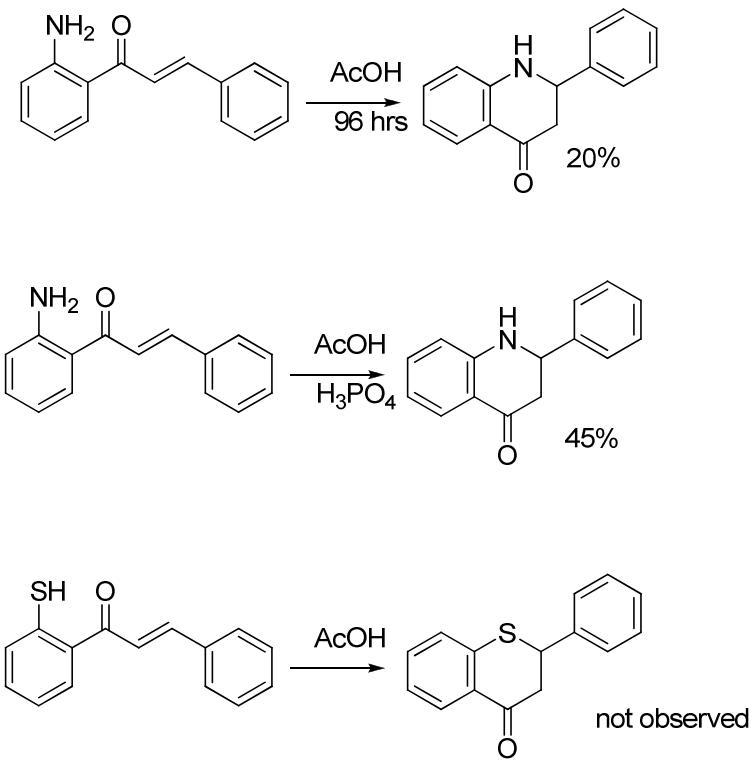
Flavanones are generally synthesized through the cyclization reaction of 2′-substituted chalcones which can itself be prepared *via* Claisen-Schmidt condensation.In this project, a library of chalcones has been synthesized following the reported methods (Marais, 2005; Narender 2007). The chalcones were prepared by reacting 2′-acetophenone, 2′-aminoacetophenone and 2′-mercaptoacetophene with various benzaldehydes. The 2′-hydroxyl- and 2′-azachalcones were purified by column chromatography and characterized by spectroscopic methods. In case of 2′-thiochalcones, attempts to isolate the pure products were unsuccessful. Presumably, thiochalcones undergo oxidative coupling easily to form the corresponding disulfides (Zolfigol *et al.*2007). However, the formation of the desired chalcone is evident in the ^{1}H NMR spectra of the crude reaction mixture. Hence, the crude mixture of the mercaptochalcones was used directly for the cyclization reaction to produce thioflavanones.

Acetic acid is one of the most convenient catalyst used in the synthesis of flavanone from 2′-hydroxchalcone (Scheme 4.1). The synthesis of flavanone began by addition of one equivalent of 2′-hydroxchalcone to glacial acetic acid (25ml per mmol of 2′-hydroxchalcone) and refluxed for 72 hrs. The reaction mixture was then poured into water and extracted with organic solvents (Cabrera *et al*.2007).

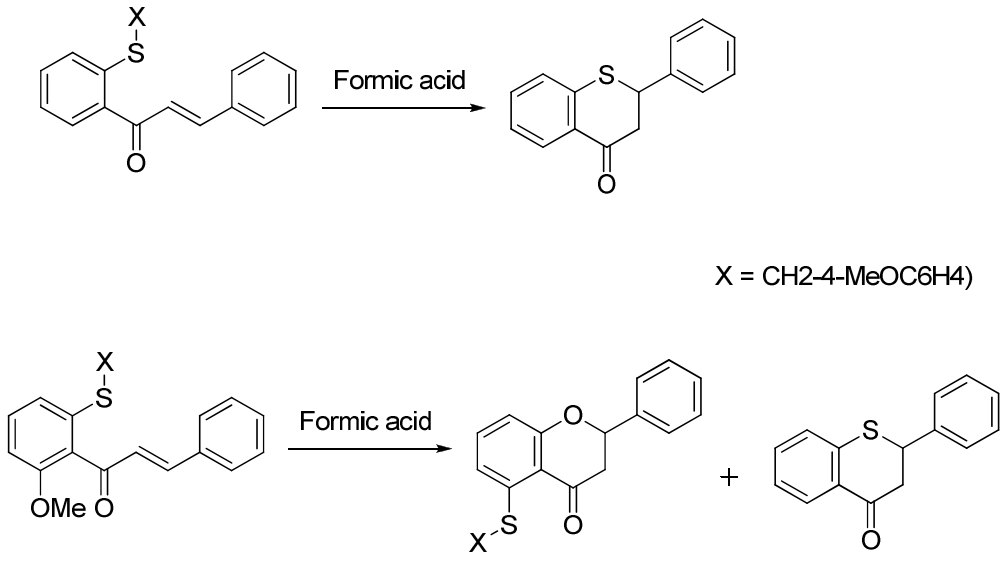


Scheme 4.1 Conventional method for synthesis of flavanones

In the synthesis of flavanones from 2′-hydroxchalcone, acetic acid was employed as the solvent and catalyst. However, for the synthesis of azaflavanone, the reaction was carried out in the mixture of phosphoric acid and acetic acid (1:1) (Wang *et al*. 2006). Refluxing 1 equivalent of 2′-aminochalcone in acetic acid alone for about 96 hrs gave only 20% yield of azaflavanone. The synthesis of thioflavanone from 2′-mercaptochalcone in acetic acid has never been reported. Unfortunately, our attempts to synthesise thioflavanones in acetic acid were also unsuccessful (Scheme 4.2). Previously, Taylor and Dean reported the synthesis of thioflavanone from protected thiochalcone in which the deprotection and cyclization of thiochalcone to the corresponding thioflavanone was carried out in formic acid (Taylor *et al.*1988). This procedure has been found to be inefficient for 5-methoxythioflavanones since the methoxy group can be partially cleaved in presence of formic acid to yield a mixture of flavanones and thioflavanones (Scheme 4.3).



Scheme 4.2 Reaction of 2′-mercaptochalcones and 2′-aminochalcones in acetic acid



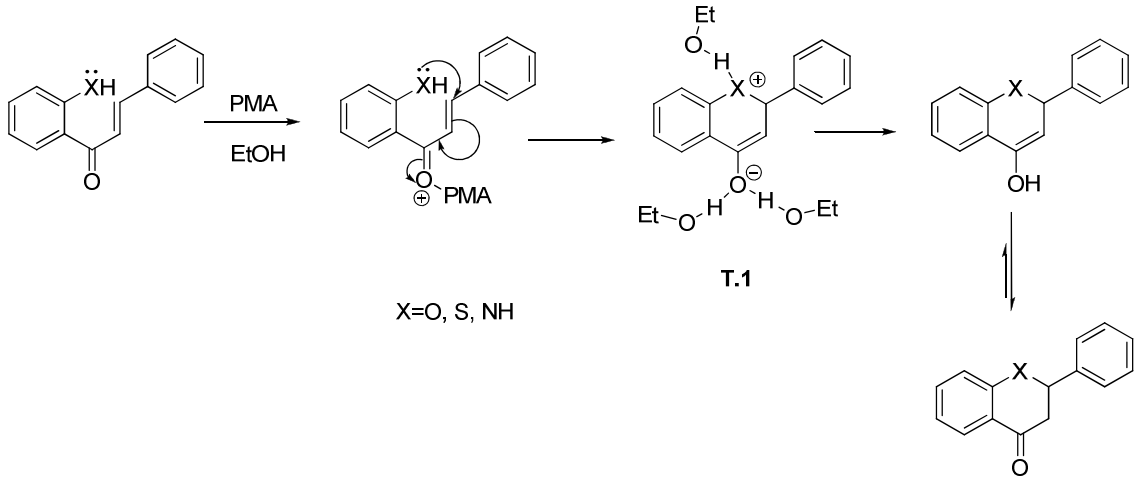
Scheme 4.3 Taylor and Dean method for thioflavanone synthesis

As mentioned in chapter 3, phosphomolybdic acid supported on silica gel (PMA/SiO_2) has been used as a catalyst in many chemical transformations such as: regioselective opening of aziridines with nucleophiles (Kumar *et al*. 2004), chemoselective hydrolysis of acetonides (Yadav *et al*.2005), Ferrier rearrangement (Yadav *et al*.2006), selective deprotection of *tert*-butyldimethylsilylther (Kumar *et al*. 2005), and aziridination of olefins with chloramine–T (Kumar *et al*. 2004). Intrigued by above catalytic properties, we decided to examine PMA/SiO_2 as catalyst for flavanone synthesis.

PMA/SiO_2 was prepared by stirring 0.1 equivalents $H_3PMo_{12}O_{40}$ in MeOH and 0.9 equivalents of silica gel (100-200 mesh) at room temperature for about six hours. Methanol was then removed under reduced pressure, to yield the PMA/SiO_2 as a yellow solid (Kumar *et al*. 2004).

Reactions for preparation of flavanones from chalcones were screened in a variety of parameters, including solvents, temperatures, reaction time and amount of catalyst used (Table 4.1). Since the presence of hydroxyl (-OH) group at C-2′ position is a requirement for intramolecular conjugated addition in the synthesis of flavanones; 2′-hydroxychalcone was selected as a model substrate to study the reaction efficiency. As shown in Table 4.1, the nature of the solvent played a key role in the reaction. The cyclization reaction of 2′- hydroxychalcone catalytic amount of $PMA\text{-}SiO_2$ indicated that the reaction performed well in ethanol and only moderately in acetonitrile (Entries 4 and 10, Table 4.1). The difference in the reactivity of the catalyst in acetonitrile and ethanol could be explained by the difference in the nature of the solvents. Acetonitrile is a polar aprotic solvent while ethanol is a polar protic solvent. Being a protic solvent,

ethanol is capable of hydrogen bonding. This capability presumably, enhances the activity of the catalyst. On the other hand, since conversion of chalcone to flavanone is a hydrogen-transfer type reaction as shown in Scheme 4.4, the presence of protic solvents like alcoholic solvents may promote the reaction due to the hydrogen bond-donating ability of this class of solvents (Andrew *et al*. 1985).



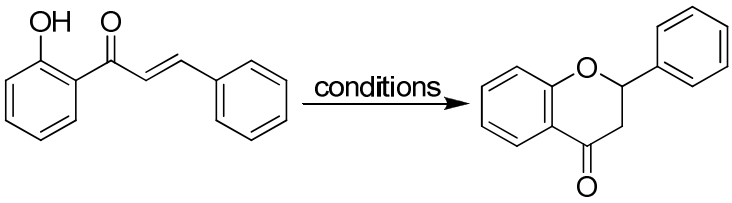
Scheme 4.4. Illustration of solvation of intermediate **T.1** by protic solvent

The reactions seemed to be temperature dependent as yields were significantly improved when reactions were performed under reflux compared to room temperature (Entries 3 and 4, Table 4.1).

The optimal quantity of the catalyst was found to be at 1 mol%. Excess amount of catalyst did not increase the yields. Under the best conditions tested, a solution of

substituted chalcones in ethanol was stirred with 1 mol% of PMA-SiO_2 under reflux to give 97% yield of flavanone (Entry 4, Table 4.1). This reaction was completed in about 8.5 hours.

Table 4.1. Screening of the reaction conditions



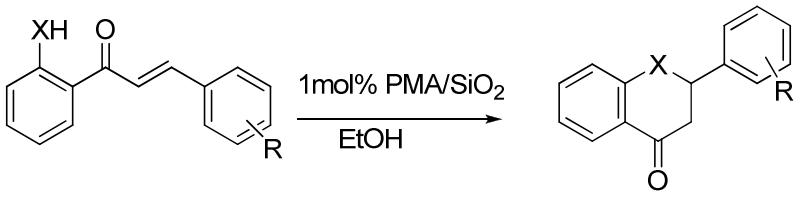
Entry	Solvent	Temperature	PMA/SiO_2 (mol %)	[a]Yield of product (%)	Reaction time(hr)
1	Ethanol	rt	-	-	48
2	Ethanol	88^0C	-	-	48
3	Ethanol	rt	1mol%	40%	48
4	Ethanol	88^0C	1mol%	97%	8.5
5	Ethanol	88^0C	5mol%	98%	8.5
6	Ethanol	88^0C	10mol%	98%	8.5
7	Acetonitile	rt	-	-	48
8	Acetonitile	88^0C	-	-	48
9	Acetonitile	rt	1mol%	15%	48
10	Acetonitile	85^0C	1mol%	32%	24
11	Acetonitile	85^0C	5mol%	35%	24
12	Acetonitile	85^0C	10mol%	42%	24

[a]Isolated yield calculated from 2′-hydroxychalcone.

Control experiments (Entries 1, 2, 7 and 8, Table 4.1) involved performing the reactions in solvent without addition of catalyst. In all cases, no product was obtained, either at room temperature or under reflux.

To study the efficiency of the catalyst, the best reaction condition for the synthesis of flavanone from 2′- hydroxychalcone (entry 4, Table 4.1) was employed for the synthesis of azaflavanone and thioflavanone from 2′-aminochalcone and 2′-

mercaptochalcone, respectively. In general, the reactions of 2′-hydroxychalcones were observed to be faster than 2′-mercaptochalcones and 2′-aminochalcones. The reaction times varied from 8.5-9 hrs for the conversion of 2′-hydroxychalcones, 9.5 hrs for 2′-mercaptochalcones and 17-22 hrs for 2′-aminochalcones to produce the desired flavanone in excellent yield (80-97%), thioflavanone (86-90%) and azaflavanone (52-68%) in moderate to good yields, respectively (Scheme 4.5).



X= O reaction time= 8.5- 9 hrs Yield= 80-97%

X= NH reaction time=17-22 hrs Yield=52-68%

X= S reaction time= 9.5 hrs Yield=86-90%

R= OMe, NO_2, Me, Cl,...

Scheme 4.5 Comparison of reaction times and yields for different type of chalcones

To explore the effect of the concentration on the yield of the different types of flavanones, the intramolecular cyclization reaction of 2′-hydroxychalcones, 2′-mercaptochalcones and 2′-aminochalcones were screened in four different concentrations (Table 4.2). The yields of flavanone analogues were observed to be influenced by the concentration of the chalcone. The optimal concentration for the transformation of chalcones to flavanones (intramolecular cyclization) was found to be 0.2M for all types of flavanones. As shown in Table 4.2, at 0.2 molar concentrations,

97% flavanone, 86% thioflavaone and 52% azaflavanone were obtained from corresponding chalcones (Entry 2, Table4.2).

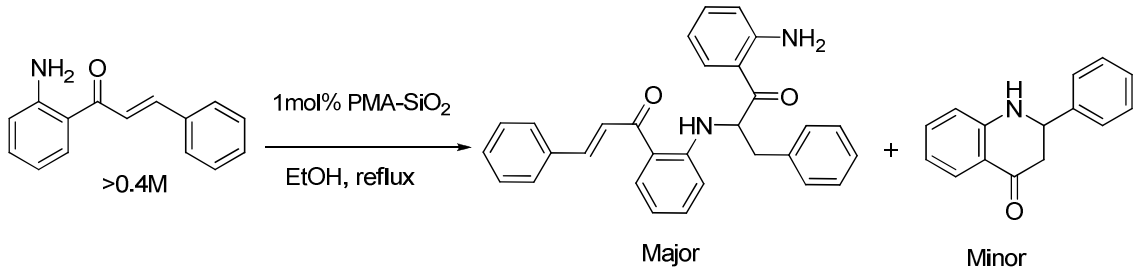
Table 4.2 Product distribution in various concentrations

Entry	Concentration (Molar)	[a]Yield of flavanone	Yield of Michael adduct	[b]Yield of thioflavanone	Yield of Michael adduct	[c]Yield of azaflavanone	Yield of Michael adduct
1	0.1	92%	2%	75%	5%	30%	5%
2	0.2	97%	2%	86%	7%	52%	10%
3	0.4	85%	7%	55%	10%	40%	32%
4	1	55%	20%	35%	15%	15%	70%

[a]Isolated yield calculated from 2′-hydroxycchalcon (estimated from ^{1}HNMR spectroscopy of crude mixture)
[b] Isolated yield calculated from 2′-thiochalcone (estimated from ^{1}HNMR spectroscopy of crude mixture)
[c]Isolated yield calculated from 2′-aminocchalcone

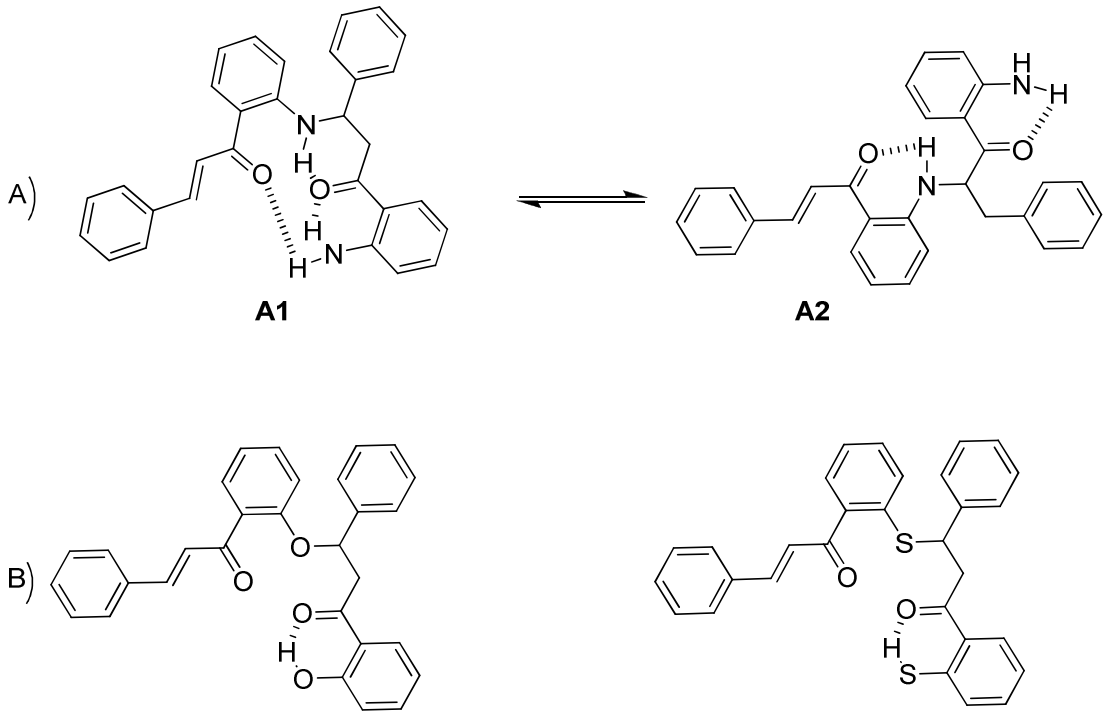
However, increasing the concentration of the chalcone (> 0.2M) seemed to promote more intermolecular chalcone-chalcone reactions. Due to the high concentration of reactants the probablity of intermolecular collision is higher which result in an increase in Michael adduct being form in all cases. As an example, in the case of 2′-hydroxychalcone, an increase in concentration from 0.2 M to 1.0 M resulted in an enhancement of Michael adduct yield by ten times. Likewise, by increasing the concentration of 2′-thiochalcone from 0.2M to 1.0 M, the intermolecular reaction of was promoted from 7% to 15%. However, this concentration effect resulting in intermolecular reaction was observed to be more pronounced in the case of

azaflavanones. As seen in Entry 4 (Table 4.2), refluxing 1M 2′-aminochalcones gave the Michael adduct as a major product with 70% yield (Scheme 4.6).



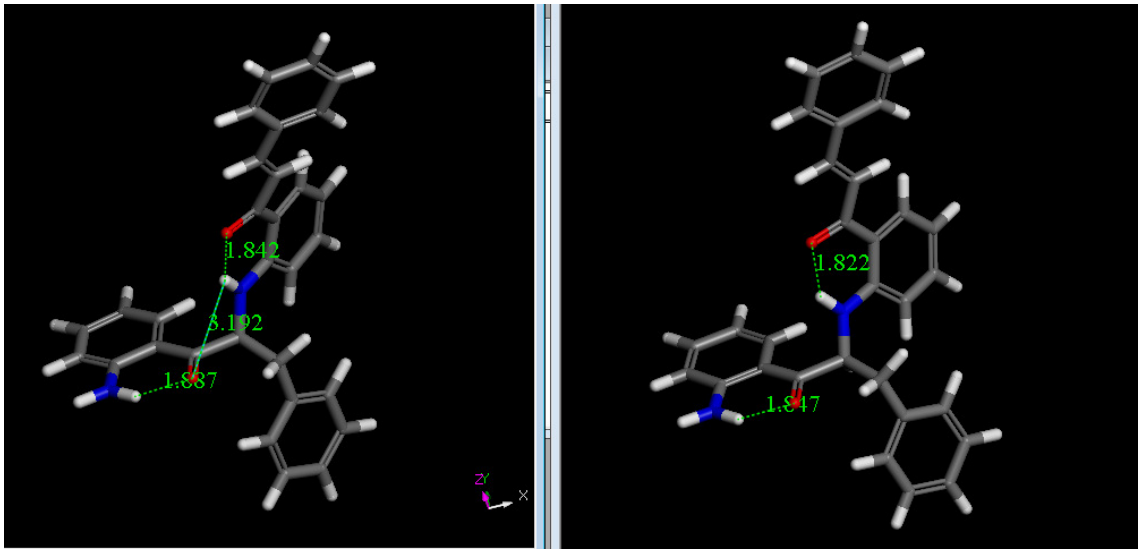
Scheme 4.6 Effect of the concentration in yield of the reaction of 2′-aminochalcone in PMA-SiO_2

Presumably, this is due to the hydrogen bond stabilization of the Michael addition product. As shown in part A, Scheme 4.7, in the case of 2′-aminochalcone, the Michael adduct could be stabilized by three (A1) or two (A2) hydrogen bonds while in the case of 2′-hydroxychalcone and 2′-thiochalcone, B, the Micheal addition products were only stabilized by one hydrogen bond. This may possibly affect the yields of intermolecular reaction products in case of 2′-aminochalcone as compare to 2′-hydroxyl and 2′-thiochalcone.



Scheme 4.7 Stabilization of conformations of intermolecular Micheal addition products of 2′-aminochalcone (A), 2′-hydroxychalcone and 2′-thiochalcone (B)

In order to compare the stability of A1 and A2, both structures were subjected to quantum calculation. Initial structure of the A1 and A2 were built and optimized with density functional theory (DFT) with double–numeric quality basis set (DN basis set) using Material Studio 4.4. As it shown in Figure 4.1, structure A1 with three hydrogen bonds is relatively more stable than A2 which has two hydrogen bonds. Although this energy gap is not very large (0.00119 Hartree = 0.74 kcal/mol), this result could still explain the preference of structure A1.



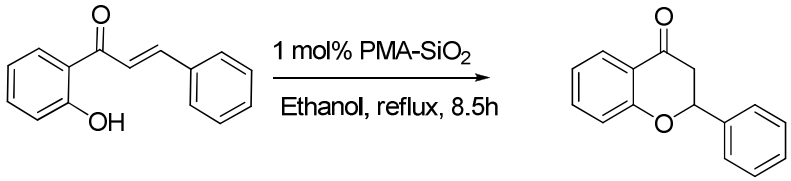
A1 = -1418.2345022 Ha A2= -1418.2356818 Ha

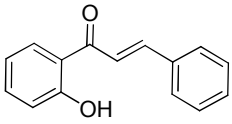
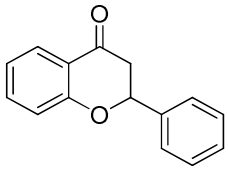
Figure 4.1 Illustration of H-bonding in A1 and A2

All the reactions occurred smoothly in 1 mol% PMA-SiO_2 in ethanol. The reaction of chalcones without 2′- hydroxyl, 2′- amino and 2′- mercapto substituent did not produce the corresponding flavanone. This seemed to indicate that presence of heteroatom substituent at C-2′ on the chalcone is required for intramolecular cyclization to occur. 2′-Hydroxychalcones reacted faster than 2′-mercaptochalcones and 2′-aminochalcones to give the corresponding flavanones in excellent to moderate yield. The low reactivity of mercapto chalcones may be attributed to the fact that thiols are easily oxidized to form disulfides (Zolfigol *et al.*2007). However, the reaction time for mercaptochalcones is not significantly longer than hydroxychalcones; lower yields of product were obtained with the mercaptochalcones even after stirring for a longer time.

Following the completion of the reaction, the catalyst was recovered with a simple workup and filtration for further reuse. As shown in Table 4.3, the recovered catalyst did not show appreciable loss in its activity since more than 89% yield of the flavanone was obtained even when the catalyst was reused for the third time (Table 4.3).

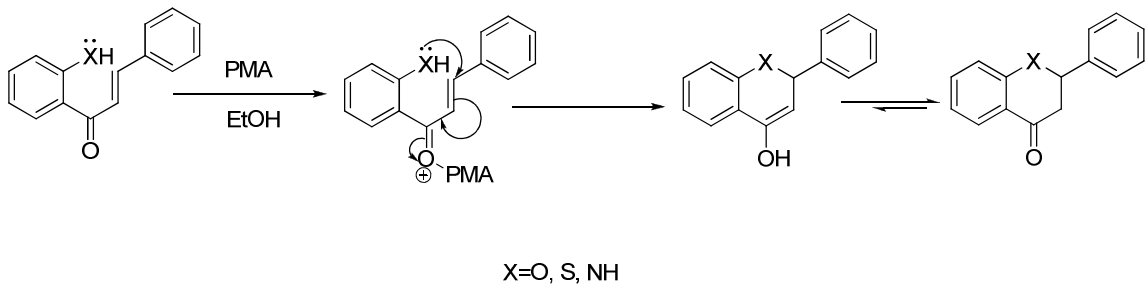
Table 4.3. The cyclization of 2-hydroxychalcone catalyzed by PMA-SiO_2 and catalyst recycle



Substrate	Product	Condition	[a]Yield
		1 mol% PMA-SiO_2, reflux, 8.5 h	97%
		1st recycle, reflux, 8.5 h	95%
		2nd recycle, reflux, 8.5h	89%

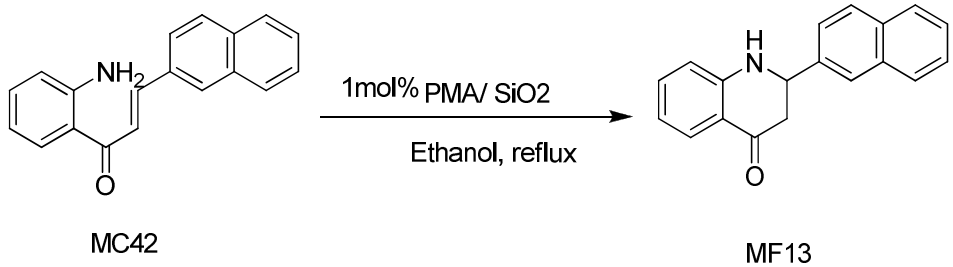
[a]Isolated yield calculated from 2′-hydroxychalcone

The plausible mechanism for the intramolecular cyclization of bicyclic 2′-hydroxychalcones, 2′-mercaptochalcones and 2′-aminochalcones into tricyclic flavanones in PMA-SiO_2 is shown in Scheme 4.8. The reaction was possibly initiated by addition of PMA to the carbonyl oxygen followed by intramolecular conjugation addition to form a tricyclic enol which preferably tautomerized to the corresponding ketone.



Scheme 4.8 Proposed mechanism for the synthesis of flavanones in PMA-SiO_2

In summary, an efficient synthetic route was developed by using PMA-SiO_2 a reusable catalyst for the cyclization of various chalcones to flavanones as a part of this study. The simple protocol, low cost of the catalyst, reusability and environmental considerations make this method useful and attractive (Sakirolah & Yaeghoobi, *et al*., 2011). Subsequently, this method was used for the preparation of various flavanone derivatives that are used for biological activity testing. For example, as shown in the Scheme 4.9, flavanone MF13 has been synthesized from chalcone MC42 using this method (see chapter 5).



Scheme 4.9 Conversion of chalcone MC42 to flavanone MF13 using 1mol% PMA / SiO_2

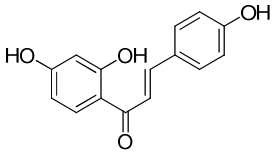
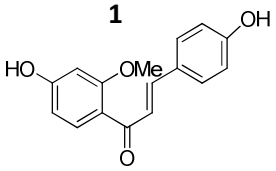
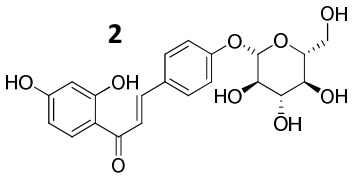
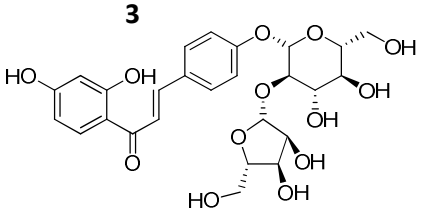
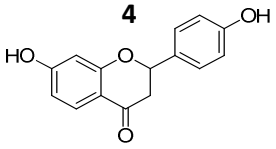
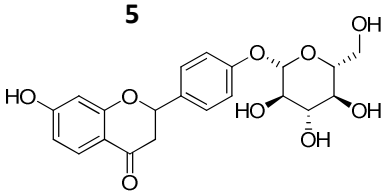
CHAPTER 5

FLAVONOID ANALOGUES WITH POTENTIAL NEURAMINIDASE INHIBITION EFFECT

In the last decade, a number of investigations have been accomplished on flavonoids for their potential neuraminidase inhibitory effect. However, most of researches were conducted on naturally occurring flavonoids. Amongst all subtypes of flavonoids, chalcones have not been extensively studied for their potency as NA inhibitors. In addition, structure-activity relationships for the chalcones have not been well studied.

Investigation by Ryu and co workers on the inhibition effect of extracted flavonoids from *Sophora flavescensa* and *Glycyrrhiza uralensis* showed isolated flavonoids to be fairly potent with IC_{50} value of 20 μM or below in all cases. The results of Lineweaver-Burk and Dixon plots suggested a non-competitive mode of inhibition. For these flavonoids, the exact binding site of neuraminidase protein and the actual mechanism of the action of these isolated flavonoids on the new receptor are still unclear. The aim of the present investigation was to explore the structural requirements for the interactions of flavonoids with the neuraminidase protein in order to deduce the potential directions for synthetic lead-optimisation studies. Preliminary structural-activity relationship information obtained showed isolated flavonoids (chalcones and flavanones) to have good to excellent activity against neuraminidase (Table 5.1; Ryu *et al*. 2008; Ryu *et al*. 2010). Hence, methoxy substitution was observed to decrease the inhibition potency. Glycosides also led to decreases in bioactivity, but hydroxyl group seemed to increase the activity (Ryu *et al.* 2010).

Table 5.1. IC_{50} and *K*i values for reference flavonoids isolated from *Glycyrrhiza uralensis* on neuraminidase activity

Compound	IC_{50} (μM)[a]	Inhibition type (*K*i μM)
	9.0 ± 0.7	Noncompetitive (9.9 ± 0.7)
1 	22.4 ± 2.2	Noncompetitive (20.1 ± 2.5)
2 	124.0 ± 2.3	Noncompetitive (94. ± 10.1)
3 	12.9 ± 1.2	Noncompetitive (15.2 ± 0.2)
4 	46.8 ± 3.3	Noncompetitive (33.1 ±10.7)
5 	82.3 ± 0.1	Noncompetitive (123.7 ±0.7)
6		

aAll compounds were examined in a set of experiments repeated three times; IC_{50} value of compounds represent the concentration that caused 50% enzyme activity loss; Oseltamivir was used as a positive control(IC_{50} value+1.59 nM) (obtaining from Ryu *et al*., 2010).

Based on the preliminary SAR information, a library of flavonoids was prepared by incorporating various substituent like OH, OMe, methylenedioxy, methyl, halogen, naphthalene, NO_2, SH, NH_2 and dimethylamine into the flavonoid structure. The general strategy to further explore this template is depicted in Figure 5.1. A library of flavonoid analogues (Table 5.2 and 5.3) was prepared in the hope to gain useful

information on the substitution of different functional groups and its molecular interactions with the neuraminidase enzyme. We focused on electron donating and electron withdrawing groups as well as hetero atoms (eg. O, N, and S) on the flavonoid backbone to study the influence of these substituent on the neuraminidase inhibition activity. Preliminary molecular modeling results suggested that the carbonyl, hydroxyl- and methoxy- substituent in the flavonids could participate in hydrogen bonding while benzene and naphthalene rings could form π interaction with the enzyme, allowing better protein- ligand interaction. In addition, 2D and 3D QSAR models indicate that, the electrostatic effect may enhance bioactivity of the chalcones while the steric influence of the substituent would diminish their potency as NA inhibitors. The 3D QSAR model also showed the importance of the position of the hydroxyl group in A ring which can influence on the hydrogen-bond donating and accepting capacities as well as the hydrophobicity which presumably would enhance the biological activity (Yeaghoobi & Frimayanti, *et al*., 2012; Unpublished result).

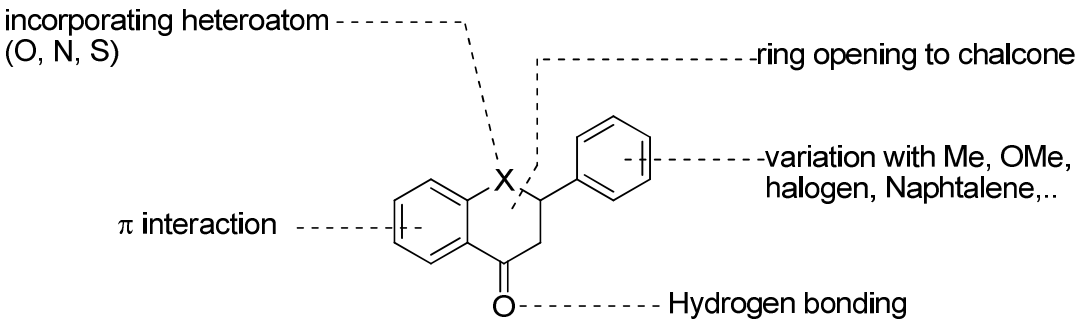


Figure 5.1 General strategies to prepare flavonoids analogues

The substituted chalcones MC1-MC50 (Table 5.2) with different functionalities were prepared *via* a Claisen-Schmidt condensation reaction between appropriate acetophenones and benzaldehydes (Marais *et al.* 2005). All compounds synthesized

were purified by chromatographic method and characterized using spectroscopic techniques except for MC47-MC50 which could not be isolated in their pure form due to the instability of mercaptochalcones during purification where thiols were oxidized to form disulfides (Zolfigol *et al.*2007; Konieczny *et al*. 1999).

Flavanones MF1-MF17 (Table 5.3) were prepared *via* an intramolecular cyclization reactation from the corresponding chalcones using catalytic amount of PMA/SiO_2 in ethanol under reflux. The resulting flavonones were then purified and characterized using spectroscopic techniques.

Chalcones MC1-MC46 and flavanones MF1-MF17 were then tested for their H1N1 neuraminidase inhibitory potency by the well known *in vitro* MUNANA assay (M. Potier *et al*. 1979). DANA (2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid), a known neuraminidase inhibitor was used as standard inhibitor (Figure 5.2)

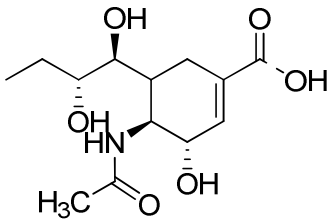
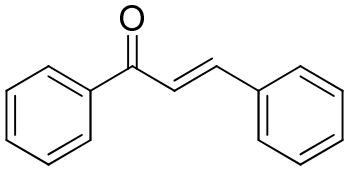
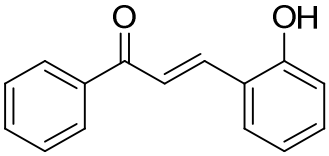
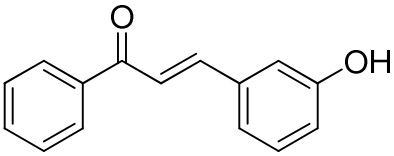
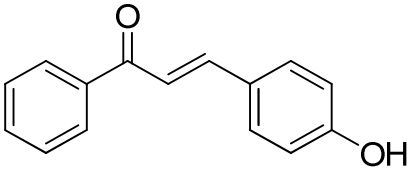
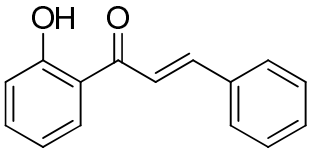
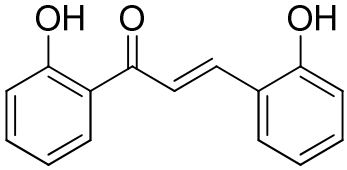
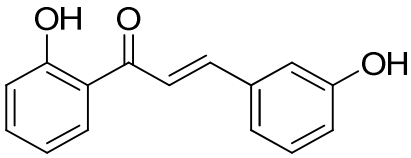
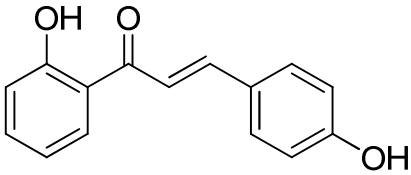
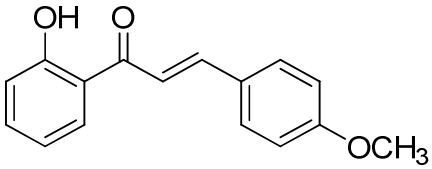
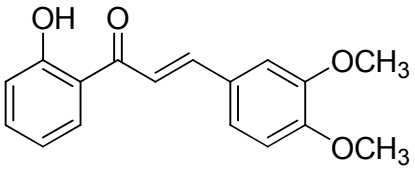
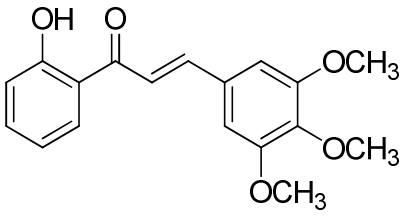
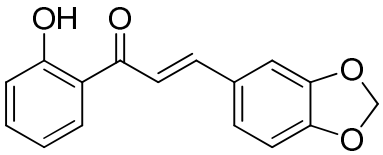


Figure 5.2. Structure of DANA

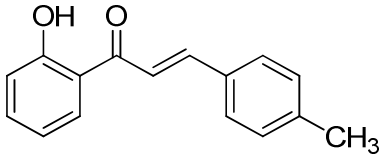
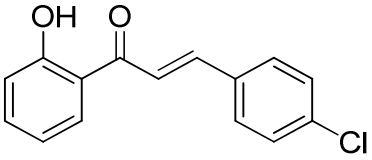
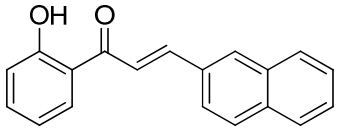
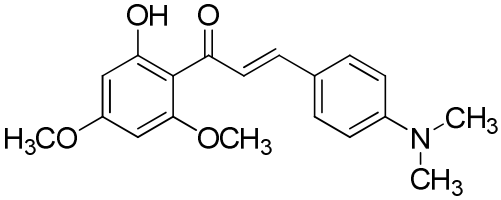
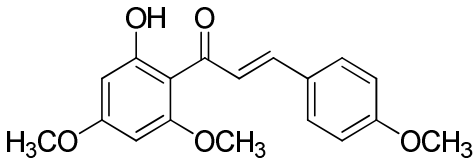
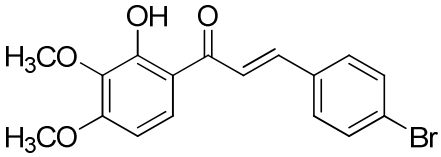
Table 5.2. Yields and melting points of chalcones synthesised

Entry	Structure	Yield [a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC1		78	55-56	56-57
MC2		82	149-150	153-154
MC3		65	152-154	156-158
MC4		45	159-160	163-165
MC5		91	89-90	86-87
MC6		53	158-159	160-161

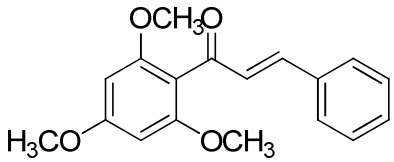
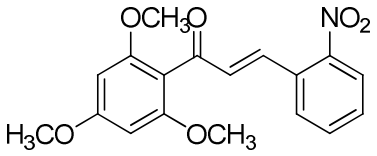
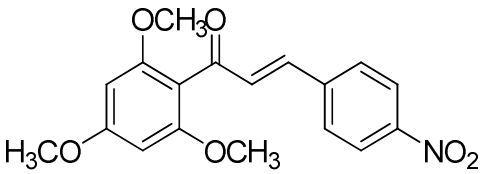
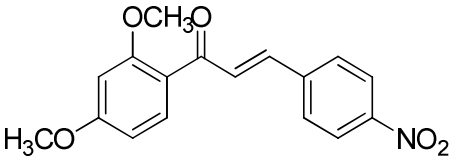
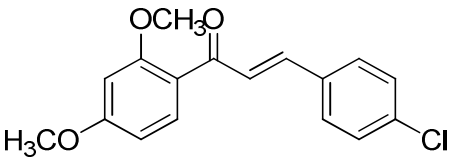
'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC7		65	148-149	150-153
MC8		53	135-137	138-139
MC9		87	91-92	93-94
MC10		92	115-117	112-113
MC11		85	158-159	152
MC12		82	135-137	138

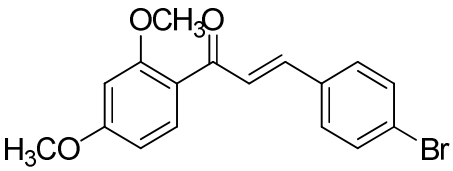
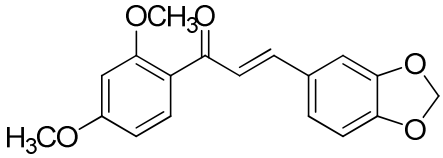
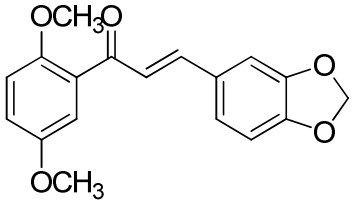
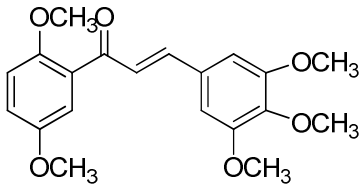
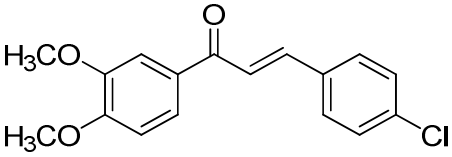
'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC13		85	115-117	117-118
MC14		56	149-152	153-156
MC15		78	135-137	135-137
MC16		72	138-140	-
MC17		75	110-112	112-114
MC18		65	152-154	-

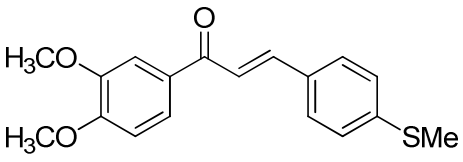
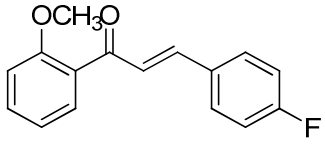
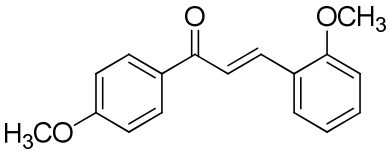
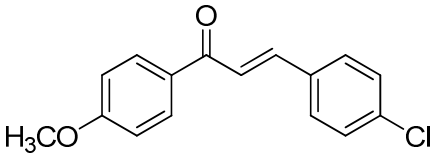
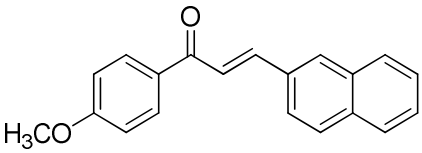
'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC19		75	-[b]	-[b]
MC20		54	152-153	-
MC21		65	158-159	-
MC22		67	182-185	191
MC23		55	125-126	118-120

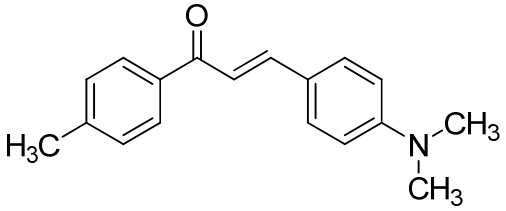
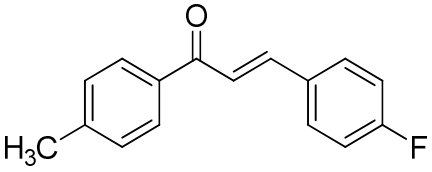
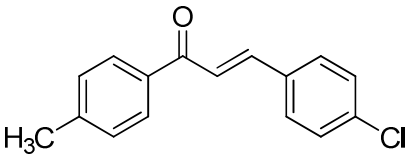
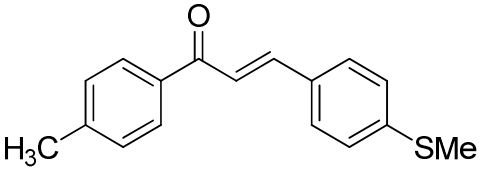
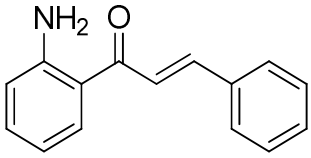
'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC24		85	112-114	-
MC25		75	119-122	123-125
MC26		75	112-114	-
MC27		82	123-125	-
MC28		45	101-103	104-106

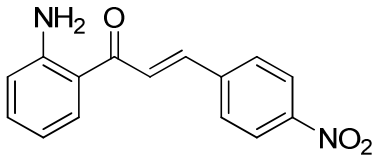
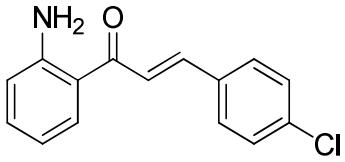
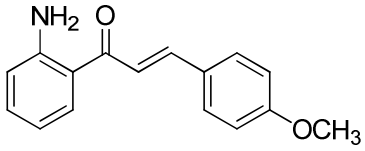
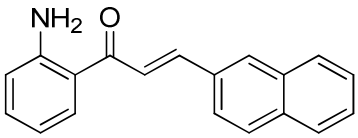
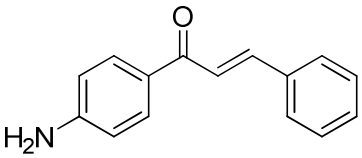
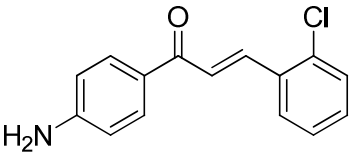
'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC29		52	92-94	-
MC30		83	107-10	-
MC31		65	51-52	44-45
MC32		65	135-136	129-131
MC33		75	155-156	148-151

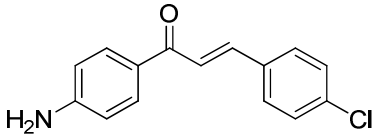
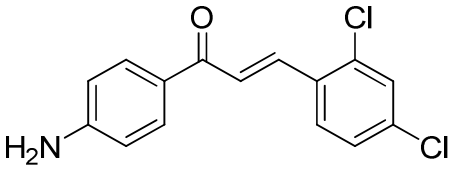
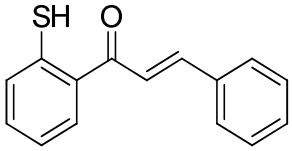
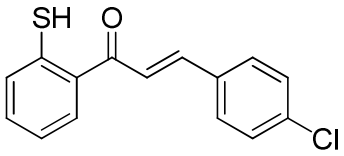
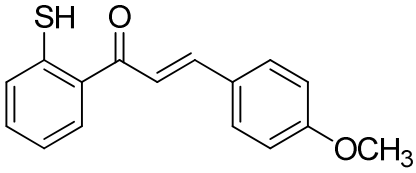
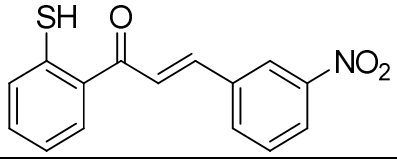
'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC34		52	132-133	-
MC35		45	145-148	151-152
MC36		47	144-146	148-150
MC37		54	142-144	-
MC38		65	66-68	70-71

'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC39		63	156-157	150
MC40		58	143-145	-
MC41		72	152-153	-
MC42		87	148-149	-
MC43		52	172-173	180-182
MC44		72	104-106	108

'**Table 5.2**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MC45		75	162-163	158
MC46		68	184-186	180
MC47		42	-[c]	-[c]
MC48		35	-[c]	-[c]
MC49		47	-[c]	-[c]
MC50		32	-[c]	-[c]

All products were identified by NMR spectroscopy
a Isolated yield; *b* Chalcones are in liquid form
c the melting point could not be obtained since the crude mixture subjected to the cyclization

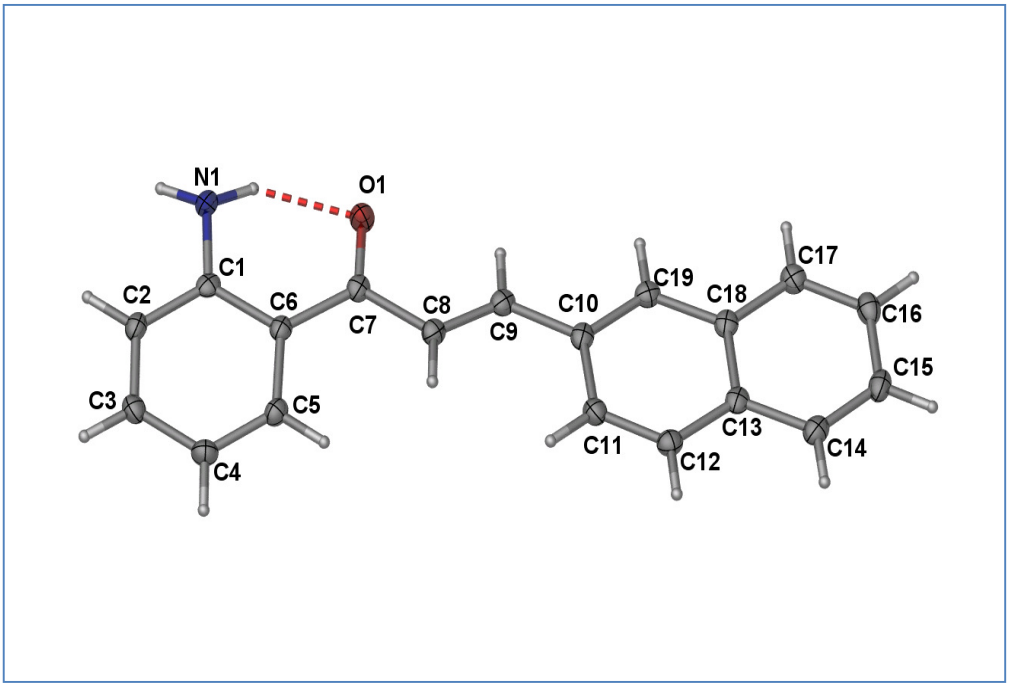
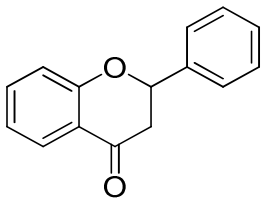
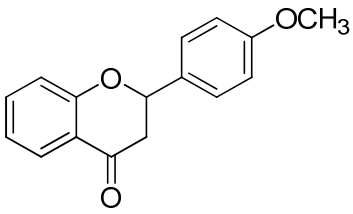
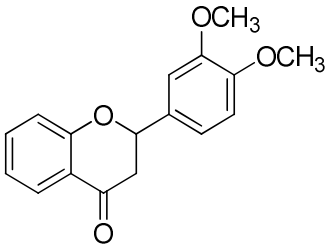
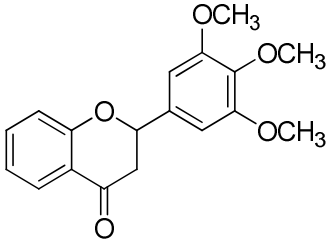
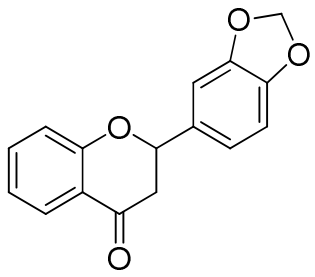
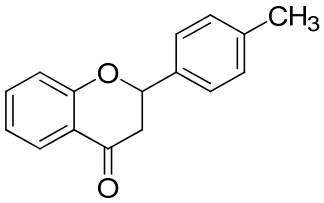
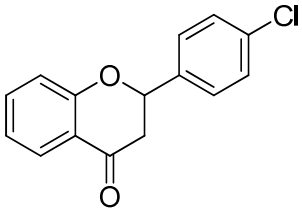
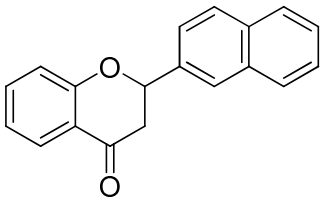
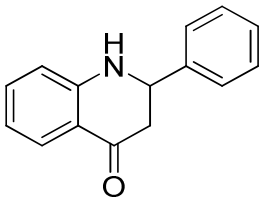


Figure 5.3. X-ray crystal structure of (*E*)-1-(2-aminophenyl)-3-(naphthalen-2-yl) prop-2-en-1-one with thermal ellipsoids at 50% probability. Atoms are labeled anonymously. Crystallographic data can be referred from appendix C.

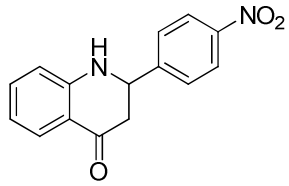
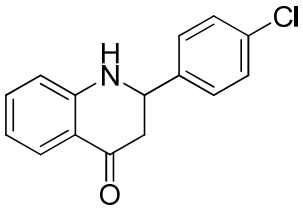
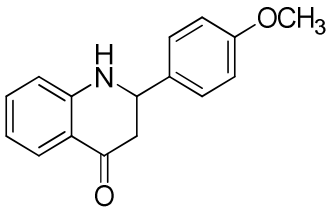
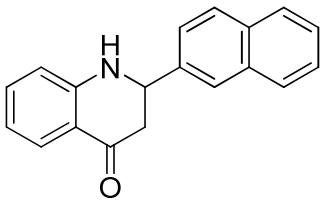
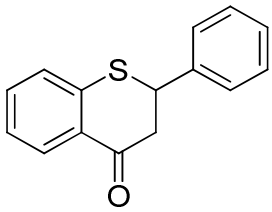
Table 5.3 Yields and melting points of flavanones synthesised

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MF1		97	95-97	97
MF2		94	153-155	155-158
MF3		93	152-153	154
MF4		88	136-138	132-133

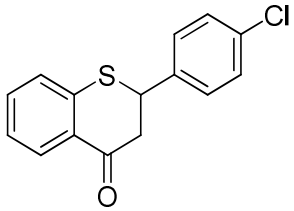
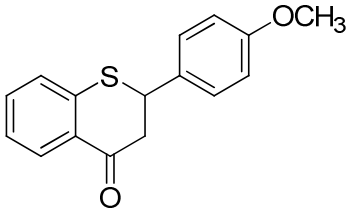
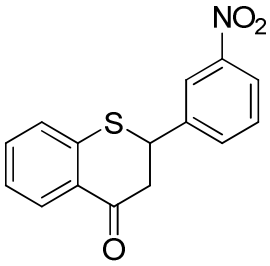
'**Table 5.3**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MF5		94	127-128	127-128
MF6		89	86-87	82-83
MF7		96	185-187	185-187
MF8		92	188-189	-
MF9		52	145-147	149-150

'**Table 5.3**. continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reprted
MF10		68	193-195	200-202
MF11		72	171-172	168
MF12		55	149-151	147
MF13		75	233-235	-
MF14		86	52-55	56-57

'**Table 5.3**, continued'

Entry	Structure	Yield[a] (%)	mp(^{0}C) found	mp(^{0}C) reported
MF15		88	122-123	126-127
MF16		84	97-99	93-94
MF17		90	112-115	116-117

[a] Isolated yield. All products were identified by ^{1}H and ^{13}C-NMR

Flavonoids as potential Neuraminidase inhibitors:

Chalcones MC1-MC46 have been docked to the neuraminidase of A/ Breving Mission/ 1/1918 H1N1 strain in complex with zanamivir (PDB ID = 3B7E, obtained from protein data bank, http://www.pdb.org). To evaluate our synthesized compounds for their potential H1N1 activity, the chalcones prepared have been tested against neuraminidase. In addition, docking studies between the chalcones and the active site of NA were carried out using Cdocker (Discovery Studio 2.5, Accelrys). The Cdocker energy reflects the interaction energy for the ligand-protein complex and the lower energy means the interaction is more stable. The result of bioassay (percentage of inhibition in 1000 μm) and Cdocker energy is summarized in Table 5.4. The calculated Cdocker energy for MC2, MC4, MC6, MC7, MC8, MC16, MC18, MC29, MC34, MC36, MC37, MC39, MC43 and MC46 showed relatively low Cdocker interaction energy (DANA is standard with -46.11 kcal/mol). This seemed to corroborate with the experimental data which showed moderate to excellent activities of these compounds against neuraminidase (ranging between 42.9 to 94.7%). In addition, MC1, MC5 and MC15 which showed relatively higher Cdocker interaction energy did not show good H1N1 inhibition activities. However, in some cases, the Cdocker energy calculation was not in agreement with the bioassay. As an example, in case of MC3, MC9-14, MC19-28, MC30-33, MC38, MC40, MC41 and MC45 the Cdocker interaction energy was found to be low (ranging between -43.25 to -31.19 kcal/mol), but their bioassay results did not show these chalcones to be active against neuraminidase.

Table 5.4 Chalcone activity against Neuraminidase

Entry	(-) Cdocker interaction energy[a,b] (kcal/mol)	Inhibition in 1000µm (%)[c]
MC1	28.25	6.9
MC2	31.80	70.1
MC3	35.69	39.6
MC4	29.74	92.1
MC5	28.08	12.9
MC6	36.94	88.6
MC7	33.04	46.7
MC8	36.94	94.7
MC9	35.35	20.1
MC10	38.65	20.2
MC11	43.25	12.9
MC12	35.41	19.5

'**Table 5.4**, continued'

Entry	(-) Cdocker interaction energy[a,b] (kcal/mol)	Inhibition in 1000µm (%)[c]
MC13	32.54	17.0
MC14	35.37	15.2
MC15	29.25	16.4
MC16	43.05	93.4
MC17	45.41	25.14
MC18	41.32	58.2
MC19	38.39	30.5
MC20	37.21	12.9
MC21	40.40	20.1
MC22	38.58	21.9
MC23	39.28	11.5
MC24	38.12	15.4

'**Table 5.4**, continued'

Entry	(-) Cdocker interaction energy[a,b] (kcal/mol)	Inhibition in 1000µm (%)[c]
MC25	35.31	19.1
MC26	35.31	20.9
MC27	46.85	37.5
MC28	39.12	16.2
MC29	41.97	43.7
MC30	32.22	31.2
MC31	31.38	22.4
MC32	38.12	12.1
MC33	33.82	19.5
MC34	33.22	65.3
MC35	29.85	42.5
MC36	32.40	55.7

'**Table 5.4**, continued'

Entry	(-) Cdocker interaction energy[a,b] (kcal/mol)	Inhibition in 1000µm (%)[c]
MC37	33.47	42.9
MC38	31.74	34.9
MC39	31.60	63.6
MC40	35.85	26.4
MC41	35.78	19.1
MC42	31.19	6.8
MC43	30.32	75.4
MC44	27.82	41.2
MC45	33.26	36.6
MC46	35.29	54

[a] Calculation performed by **Frimayanti** *et al.* using Cdocker (Discovery Studio 2.5, Accelrys) ;
[b] Enzym: 3b7E (Neuraminidase of A/ Breving Mission/ 1/1918 H1N1 strain in complex with zanamivir;
[c] Bioassay performed by **Ikram** *et al.* using DANA as standard with -46.11 kcal/molCdocker interaction energy

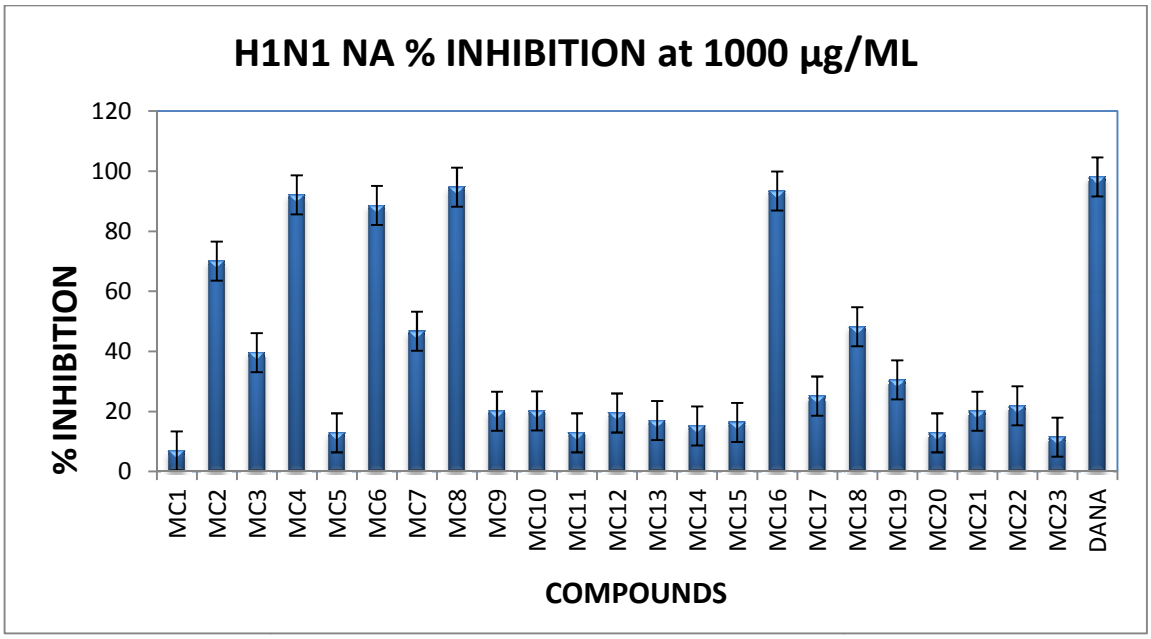
Flavanones MF1-MF17 have been also docked to the neuraminidase of A/ Breving Mission/ 1/1918 H1N1 strain in complex with zanamivir (PDB ID = 3B7E, obtained from protein data bank, http://www.pdb.org). To validate the computational observations for the potential of these flavanones have been tested against neuraminidase. The result of bioassay (percentage of inhibition in 250µm) and Cdocker energy is summarized in Tables 5.5. The bioassay results did not show good activity although, the calculated Cdocker interaction energy for MF3, MF4, MF5 and MF10 was found to be relatively low (ranged from -30.82 to -31.45 kcal/mol). This observation may be due to the binding of flavanones as ligand to the allosteric site rather than the active sites (Ryu *et al.* 2008). Bioassay results of chacone and flavanone analogues are shown in Table 5.6 and Table 5.7 respectively.

Table 5.5 Flavanone activity against Neuraminidase

Entry	(-) Cdocker interaction energy[a,b] (kcal/mol)	Inhibition in 250µm (%)[c]
MF1	26.22	8.2
MF2	27.04	11
MF3	31.45	12
MF4	30.86	14.7
MF5	30.82	10.7
MF6	27.16	8.0
MF7	25.89	1.8
MF8	28.48	6.4
MF9	28.93	7.3
MF10	31.20	5.3
MF11	26.63	5.1
MF12	27.22	3.0
MF13	27.74	7.7
MF14	18.34	4.7
MF15	25.60	13.5
MF16	26.76	12.6
MF17	26.32	5.4

[a] Calculation performed by **Frimayanti** *et al.*using Cdocker (Discovery Studio 2.5, Accelrys) ;
[b] Enzym: 3b7E (Neuraminidase of A/ Breving Mission/ 1/1918 H1N1 strain in complex with zanamivir;.
[c] bioassay erformed by **Ikram** *et al.* using DANA as standard with -46.11 kcal/molCdocker interaction energy

Table 5.6 Bio assay result of chalcones



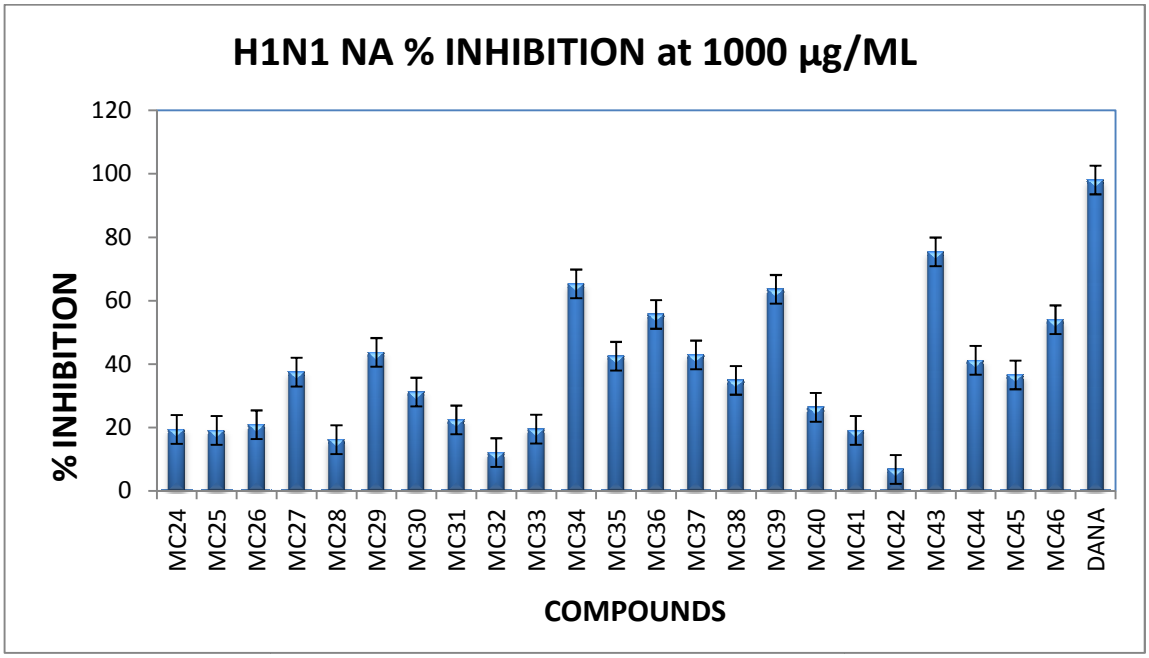
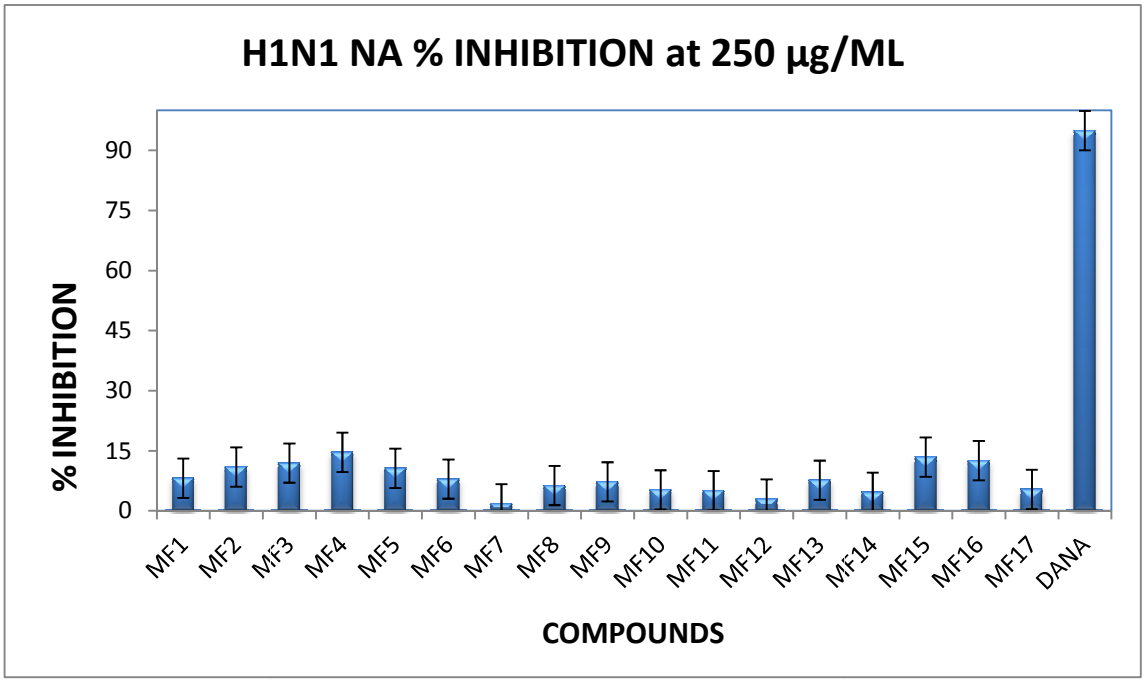


Table 5.7 Bio assay result of flavanones, azaflavanones and thioflavanones

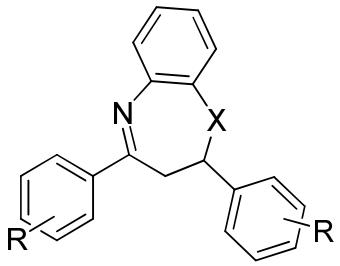


CHAPTER 6

1,5-BENZOTHIAZEPINES AND THEIR POTENTIAL HEALTH BENEFITS

Thiazepines and diazepines are seven- membered heterocyclic rings with two hetero atoms. Benzothiazepine and benzodiazepine moieties are two subgroups of this family of heterocycles in which the thiazepine or diazepine rings are fused to a benzene ring.

1,5-Benzodiazepines are an important class of organic compounds. They are effective analgesic, anti-convulsant and sedative medicines (Page *et al*. 2002) because not only they are completely absorbed but also as they are lipophilic, they can penetrate the brain easily (Fernández *et al*. 2006). Thus, this class of heterocyclic compounds continues to attract many chemists and pharmacologists since 1955 when the first benzodiazepine "Chlordiazepoxide" (Librium) was discovered by Leo Sternbach and subsequently synthesized by Hoffmann_ Laroche in 1960. Commercial "diazepam" was marketed in 1963 for the first time (Shorter *et al*. 2005). Based on molecular structures, benzothiazepines can be divided to some other subclasses, *i.e.* 1,4- benzothiazepines, 4,1- benzothiazepines and 1,5- benzothiazepines (Levai *et al*.1999). 1,5-Benzothiazepines broadly used as anti-feedant (Reddy *et al.* 1993), tranquilizer (Kugita *et al.* 1971), anti-depressant (Geyer *et al*. 1970), CNS stimulant(Kawashima *et al.*1985), calcium channel blocker (Kugita *et al.* 1971), anti-microbial agent (Dandia et al. 1998). Moreover, 1,5-benzothiazepines have been combined with other well-known pharmaceutically active compounds such as benzofuran derivatives to form a single molecule with improved pharmaceutical properties (Cherkupally *et al*. 2008). The general structure of 1,5-benzodiazepine and 1,5-benzothiazepine is shown in Figure 6.1.



X = NH, S

R= OH, OMe, Me, Halogen,...

.

Figure 6.1 General structure of 1,5- benzodiazepines and 1,5- benzothiazepines

1,5-benzodiazepines are well established in pharmacological and medicinal chemistry. However, limited number of studies had been carried out on the synthesis and SAR for 1,5-benzothiazepines, especially in terms of anti-viral activities.

6.1 Anti-viral effect:

The anti-viral effects of benzodiazepines and benzothiazepines have mainly been focused on HIV and hepatitis viruses. Nicol and co-workers showed that dibenzothiazepinethione derivatives to have anti-viral activities against Varicella-Zoster virus, hepatitis B and HIV-1 (Nicol *et al*. 1992). In another study, Delpa and co-workers showed 1,4- benzothizapines and 1,4-benzodiazepines with a peptide side-chain to have inhibitory effect on hepatitis B, and D viruses by affecting the binding of the hepatitis virus to annexin V (Delpa *et al*.2000). A group of thiazolothiazepines have also been reported to be promising candidates for the HIV treatment by targeting the integrase enzyme (Neamati *et al*. 2000). Tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-one and -thione (TIBO), are also known for their activity on HIV-1 virus (Pauwels *et al.* 1990).

A number of tricyclic derivatives of 1,4-benzothiazine and 1,5-benzothiazepine were also reported to have anti- HIV properties *in vitro* (Grandolini *et al.*1999). In addition, 2H-pyrrolo [3,4-b] [1,5] benzothiazepine derivatives were also reported to be potent candidates for HIV-1 (Di Santo *et al*. 2005).

Our recent interest in 1,5-benzothiazepines has been inspired by the anti-viral properties of this class of compounds. Thus, in this study we explored on neuraminidase inhibitory activity of this class of heterocycles.

6.2 Platelet aggregation inhibitory effect:

Platelet aggregation is a process in which platelets in the blood will clump together. This process can eventually lead to the formation of clot in the blood vessels and cause cerebral vascular complications. Few 1,5-benzothiazepine derivatives bearing N-amino groups (Figure 6.2) have been reported to have potent platelet aggregation caused by platelet activating effectors, collagen, epinephrine and arachidonic acid (Bariwal *et al*. 2008).

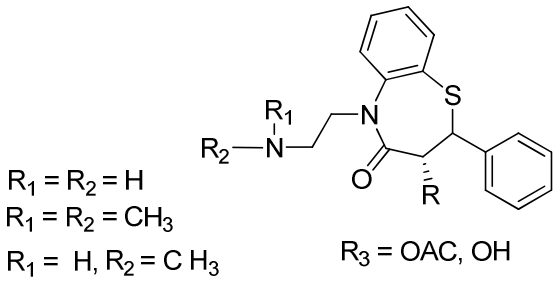


Figure 6.2 Structure of 1,5- bezothiazepines with potential anti-platelet aggregation properties

6.3 Anti-cancer effect:

The anti-cancer properties of benzothiazepine derivatives have been shown in number of studies. For example, 1,4- benzothizepine and its analogues synthesized by Garofalol and co-workers were shown to have potent anti-tumors activities against murine L1210 and human lymphoblastic CCRF_CEM leukemia cell growth (Garofalo *et al*.1993).

Evaluation of some synthesized pyrrolo[1,5]benzoxa(thia)zepine analogues against tumor cell showed these compounds to be promising potent apoptotic agents (Mc Gee et al. 2005). 1,4-Benzodiazepine-2,5-diones was also reported to exhibit anti-tumor activity by disrupting Hdm2:p53 interaction (Marugan et al. 2006).

6.4 Anti-bacterial and anti-fungal effect:

A number of benzothiazepines have been investigated for their anti-bacterial and anti-fungal activities. A group of synthesized methylene-bis-benzofuranyl-[1,5]-benzothiazepines were found to have *in vitro* anti-bacterial activities, nearly as active as those well known anti-bacterial medicines such as streptomycin and penicillin. Substitution at the 4^{th} position of this class of benzothiazepines was observed to play a key rule in enhancing the potent bioactivity. Moreover, these compounds exhibited moderate to good anti-fungal activities (Cherkupally *et al*. 2008). 2,4-Diaryl-2,3-dihydro-1,5-benzothiazepines and their 1, 1- dioxide derivatives were also found to have anti-bacterial and anti-fungal properties (Jadhav *et al*.1983; Barot *et al*. 2001).

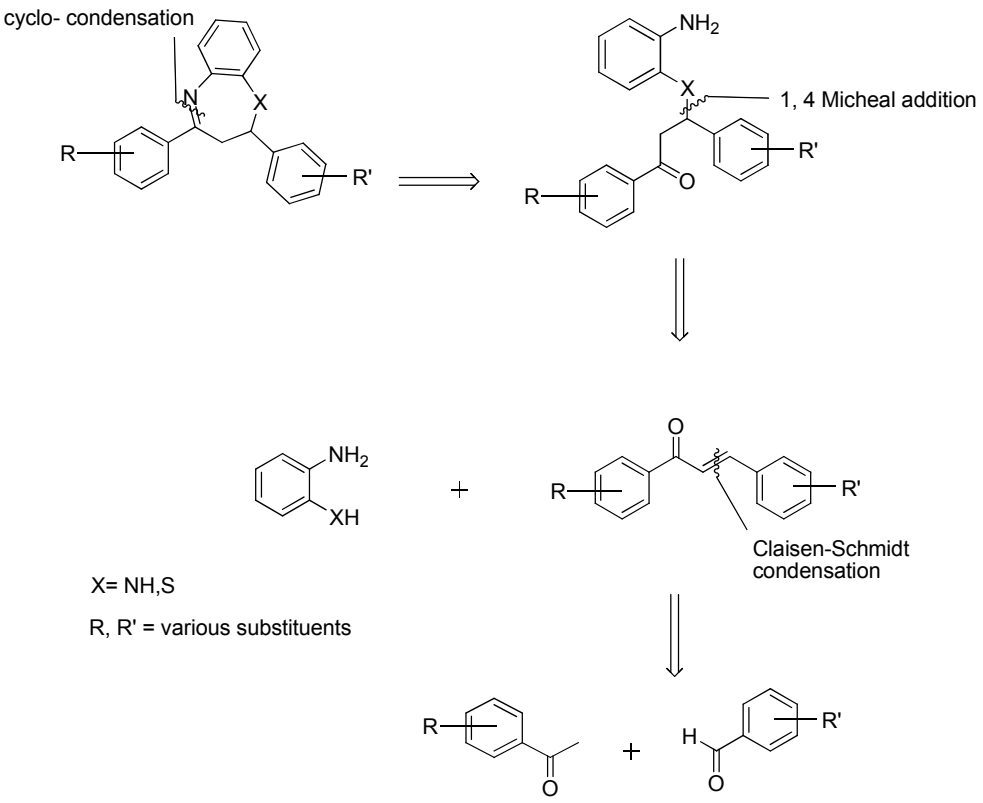
6.5 CNS activity effect:

1,5- Benzothiazepine derivatives such as thiazesim and quentiapine have been clinically approved to be effective candidates for CNS (Central Nervous System) disorders. Pyrrolo- derivatives of benzothiazepines have been shown to have excellent sedative action comparable with diazepam (Nacci *et al*. 1984). Imidazolo- derivatives were also reported to be fairly active on CNS inhibition with notable anti-inflammatory activities (Ambrogi *et al.*1995, Grandolini *et al*.1995). Furthermore, oxadiazolo-derivatives has been tested against seizures and have exhibited comparable activity to clobazam (De Sarro *et al.*1995).

CHAPTER 7

SYNTHETIC ROUTES TO THE BIOACTIVE 1,5-BENZOTHIAZEPINES

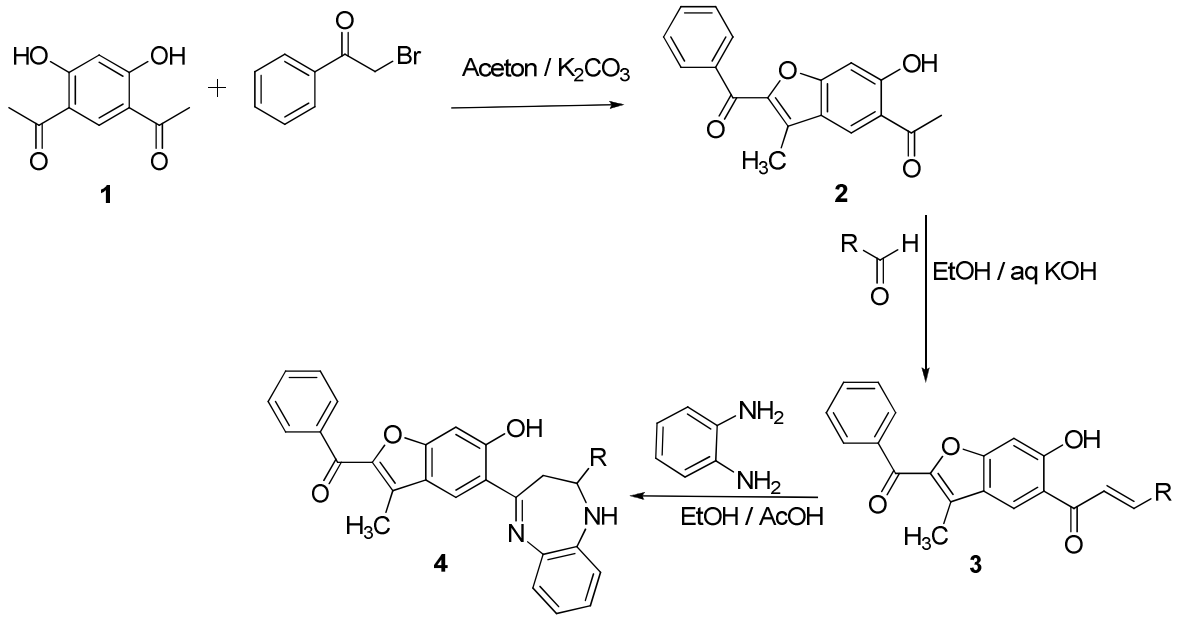
The synthesis of 1,5-benzothiazepine and its other analogue, 1,5-benzodiazepines often involve an intermolecular cyclo-condensation of *o*-aminothiophenol (*o*-ATP) and *o*-phenylenediamine (*o*-PDA) with ketones (Ried *et al.*1959), α-β-unsaturated carbonyl systems like chalcones or β-haloketones (Ried *et al.*1957). Chalcones are normally synthesized *via* Claisen-Schmidt condensation of acethophenones with various benzaldehydes (Marais, 2005; Narender and Papi Reddy 2007). As outlined in Scheme7.1, retrosynthetic analysis consists of three primary disconnections, which can provide a facile synthetic route for the synthesis of 1,5-benzothiazepines and 1,5- benzodiazepines without a lengthy protection-deprotection steps.



Scheme7.1.Retrosynthesis strategy for the synthesis of 1,5- benzothiazepines and 1,5-benzodiazepines

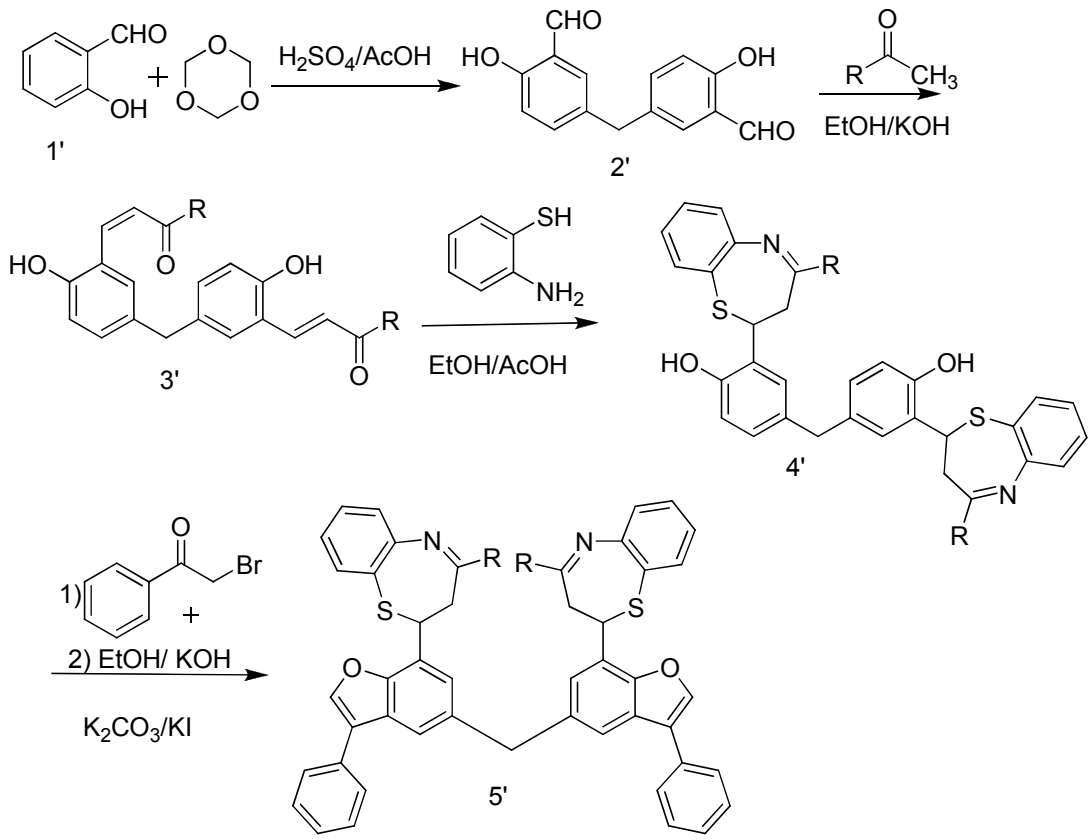
7.1 Acetic acid catalyzed azepine synthesis

Acetic acid has been reported as a mild media for the synthesis of 1,5-benzodiazepines (Reddy *et al.*2000) and 1,5-benzothiazepines (Cherkupally *et al.*2008). For the synthesis of 1,5-benzodiazepines, an equimolar of 1,1′-(4,6-dihydroxy-1,3-phenylene)diethanone, **1**, and bromoacetophenone was refluxed in an acetone solution of potassium carbonate (6 hrs). After completion of the reaction, acetone was removed and the residue was poured over ice. The solid was filtered out, washed with hot alkaline solution, and neutralized with diluted HCl. Recrystalization produced compound **2**, which was treated with the appropriate benzaldehyde through Claisen-Schmidt condensation to give the chalcone **3**. Refluxing chalcone **3** and *o*-PDA in ethanol containing a few drops of glycial acetic acid resulted in the 1,5-benzodiazepines **4.** This method is summarized in Scheme 7.2 (Reddy *et al.*2000). Later, Cherkupally and co-workers reported a similar synthetic route for the synthesis of 1,5-benzothiazepine derivatives where trioxane and salicylaldehyde**1'** were reacted in a mixture of acetic acid and concentrated sulfuric acid to produce the aldehyde **2'** which underwent Claisen-Schmidt condensation in presence of different methyl ketones to produce methylen-bis- chalcone **3'**. Reaction of chalcone **3'** with *o*-ATP yielded 1,5-benzothiazepines **4'**. To improve potential bioactivity, compound **4'** was treated with bromoacetophenone in presence of potassium carbonate followed by alkaline solution of ethanol to give **5'**. The reaction is summarized in Scheme 7.3 (Cherkupally *et al.*2008).



R= phenyl, 4 - OMe phenyl, 4- Me phenyl, 2-Cl phenyl

Scheme 7.2 Synthesis of 1,5-benzodiazepines in acetic acid

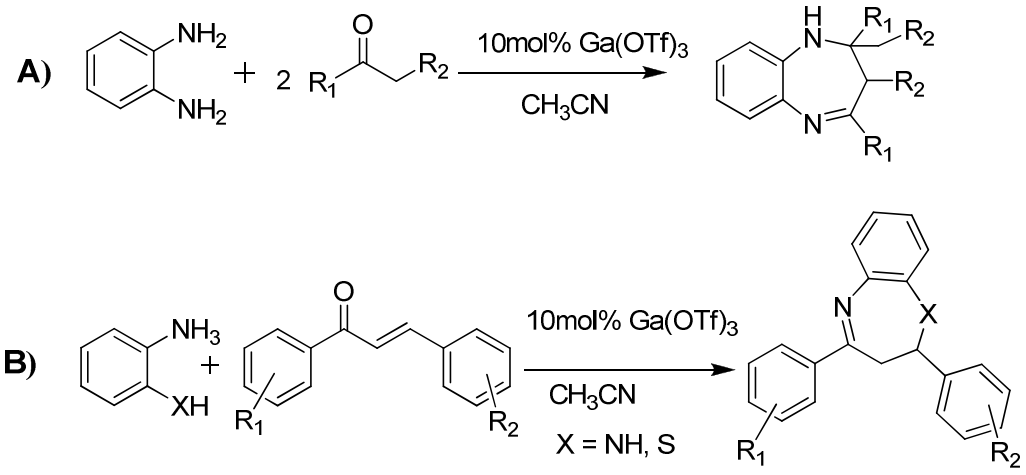


R= phenyl, 4-Cl-phenyl, 4-Br-phenyl, 4-OMe-phenyl

Scheme 7.3 Synthesis of 1,5-benzothiazepines in acetic acid

7.2 Gallium triflate catalyzed azepine synthesis

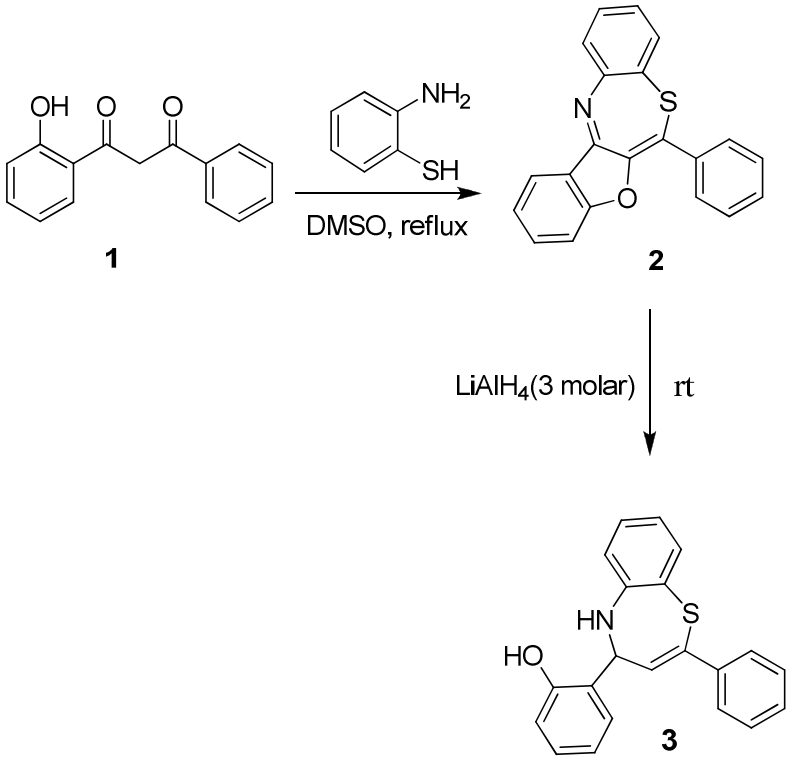
Gallium triflate, $Ga(OTf)_3$, has been used as a catalyst for azepine synthesis. It was observed to perform well in acetonitrile. This catalyst has been reported to be efficient for the synthesis of 2,2,4-trisubstituted 1,5-benzodiazepines through the reaction of 2 equivalent aromatic or aliphatic ketones with 1 equivalent *o*-PDA (Scheme 7.4, A). Moreover, $Ga(OTf)_3$ has been reported to catalyze the synthesis of 2,4-disubstituted 1,5-benzodiazepines and 1,5-benzothiazepines from 1 equivalent chalcone with *o*-PDA and *o*-ATP respectively (Scheme 7.4, B). In a typical experiment, 1 mmol of chalcones, 0.1 mmol $Ga(OTf)_3$ and *o*-PDA (1 mmol) or *o*-ATP (1.2 mmol) were refluxed in MeCN for 4-6 hrs to produce the desired 1,5-benzodiazepines and 1,5-benzothiazepines respectively (Pan *et al*. 2008).



Scheme 7.4 Synthesis of 2,2,4-trisubstituted 1,5-benzodiazepines; **A** and 2,4-disubstituted 1,5-benzodiazepines; **B** in $Ga(OTf)_3$

7.3 $LiAlH_4$ catalyzed azepine synthesis

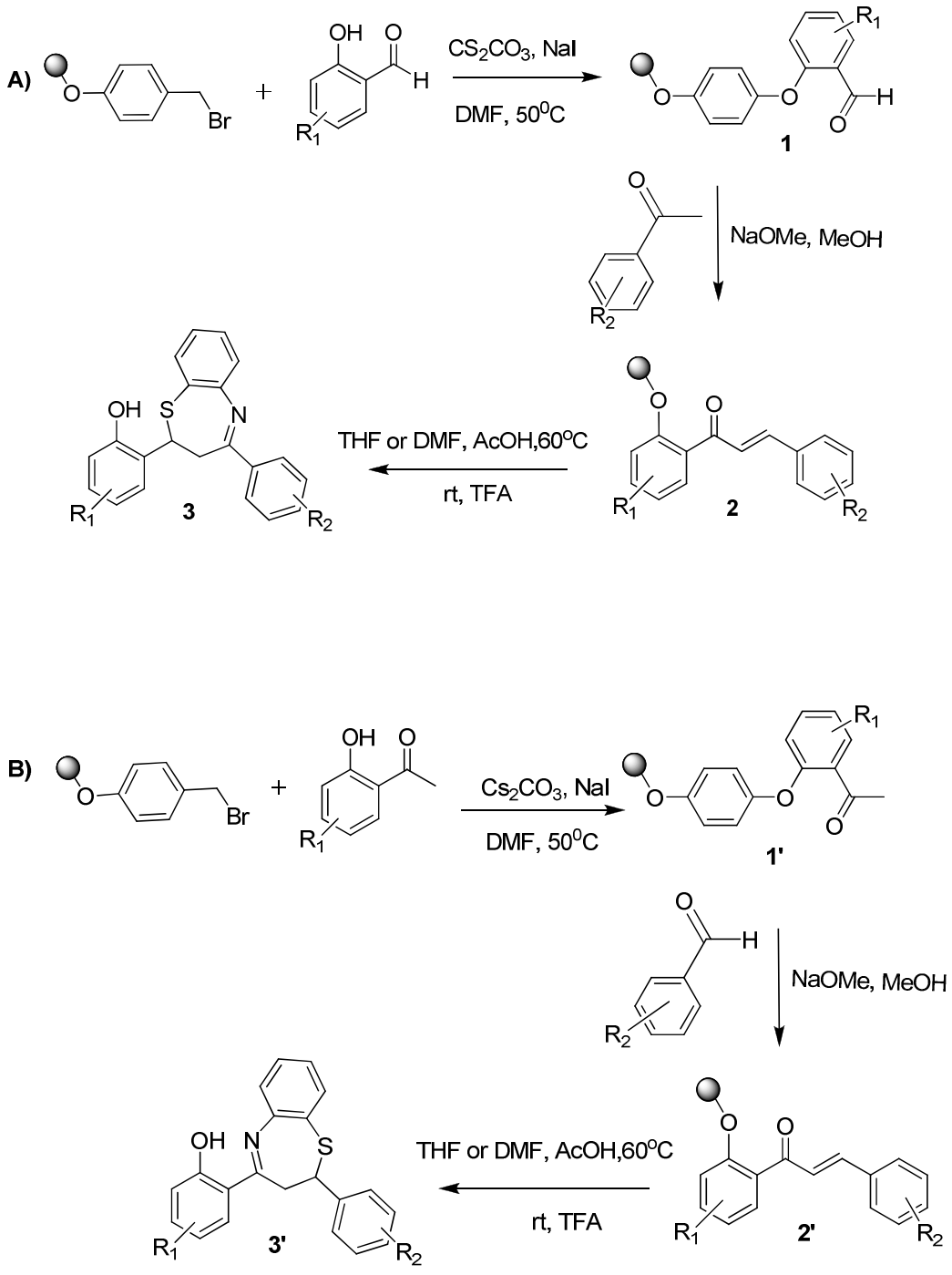
The synthesis of oxygen- bridged 1,5- benzothiazepine derivatives, **2** has been carried out by reacting *o*-ATP with phenolic *β*-ketones in DMSO under reflux condition (Scheme 7.6). The 2-phenyl-4-(2′-(-hydroxyphenyl)-4,5-dihydro-1,5-benzothiazepine derivatives (**3**, Scheme 7.5) can be produced from benzofuro-annelated 2-phenyl 1,5-benzothiazepine (**2**, Scheme 7.5), through reduction and furan ring opening. Lithium aluminum hydride **(**LAH) can catalyze this reaction at room temperature. This method enabled us to synthesize a wide range of 1,5-benzothiazepines bearing a hydroxyl group at *ortho* position by mean of synthetic protocol (Ahmad *et al*.2000).



Scheme 7.5 Synthesis of 2-Phenyl-4-(2′-(-hydroxyphenyl)-4,5-dihydro-1,5-benzothiazepines using LAH

7.4 Solid phase azepine synthesis

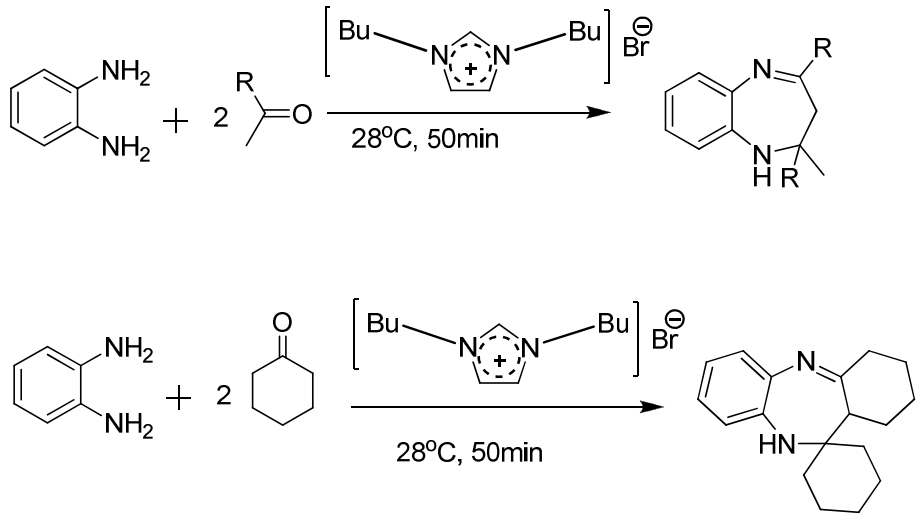
Solid phase synthesis has been reported as an alternative method to the solution-phase synthesis which can enable the synthetic chemist to prepare an acceptable amount of 1,5- benzothiazepines from functionalized chalcones by minimizing the possibility of side reactions of substitutions in benzaldehyde during chalcone synthesis. Firstly, a solution of substituted benzaldehyde in DMF needs to be treated with the Wang bromide resins in the presence of $CsCO_3$ and sodium iodide. The supported chalcone, **2**, has been synthesized by the addition of acetophenone to the alkylated compound, **1** in presence of a methanolic solution of MeONa. To synthesize 1,5-benzothiazepine, **3**, a mixture of supported chalcone and *o*-ATP have been heated in THF and treated with acetic acid followed by the cleavage of the Wang bromide in TFA / DCM (Scheme 7.6, **A**). As summarized in Scheme 7.6, B**,** similar procedure can be carried out by protecting functionalized acetophenones (Micheli *et al*. 2001).



Scheme 7.6 Solid phase synthesis of 1,5-benzothiazepines using supported benzaldehyde , **A**, and supported acetophenone, **B**.

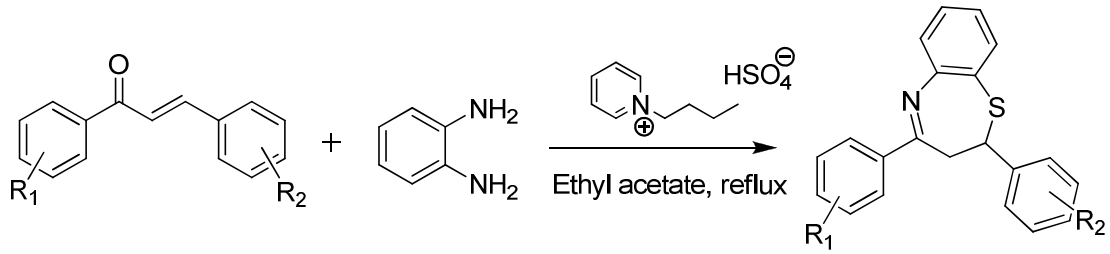
7.5 Ionic Liquid promoted 1,5-benzodiazepine synthesis

1, 3-*n*-dibutylimidazoliumbromide ([bbim] Br) is a room temperature ionic liquid which has been used to promote the synthesis of 1,5-benzodiazepines by reacting 1 equivalent *o*-PDA with 2 equivalents cyclic or acyclic ketones. This reaction is summarized in Scheme 7.7 (Jarikote *et al*. 2003).



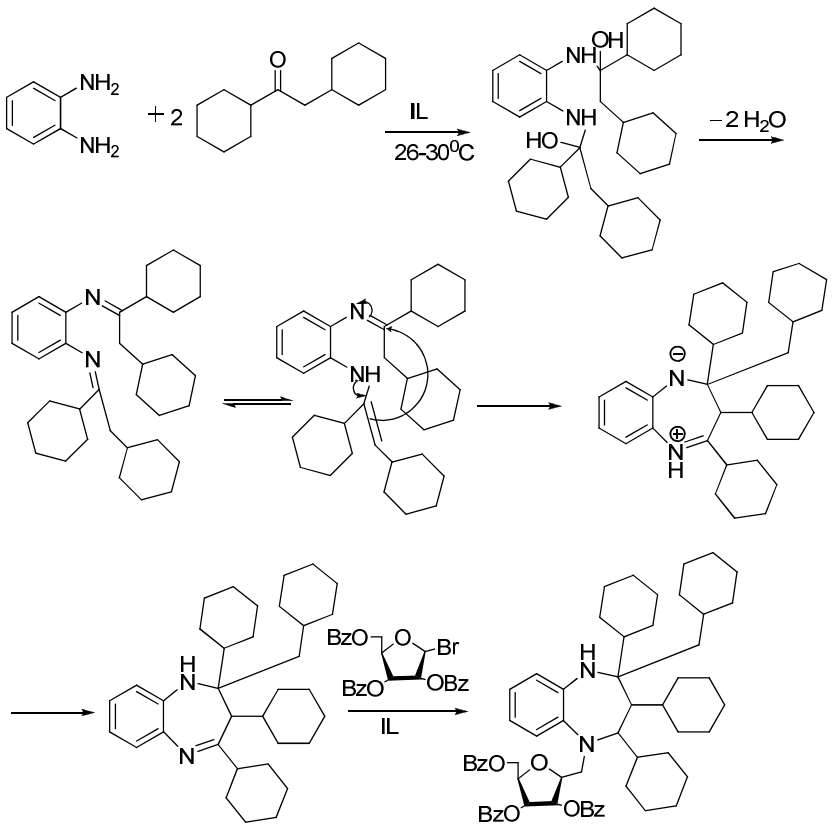
Scheme 7.7 ([bbim] Br promoted synthesis of 1,5-benzodiazepines

In a similar work, Du used 1-butylpyridinium hydrogen sulphate ([BPy] HSO_4) for the synthesis of 1,5-benzodiazepines from chalcones and *o*-PDA. In this method, a mixture of 1 equivalent chalcone, 1.5 equivalent *o*-PDA and catalytic amount of [BPy] HSO_4 were refluxed in ethyl acetate. After completion of the reaction, the reaction mixture was added to MeOH, filtered and the crude was purified by column chromatography to give the desired benzodiazepine in 69% yield (Du *et al.* 2006). The reaction is summarized in Scheme 7.8.



Scheme 7.8 [BPy] HSO_4 promoted synthesis of 1,5-benzodiazepines

Recently, Yadav and co-workers reported the synthesis of 1,5-benzodiazepine ribofuranosides by using various imidazolium salt ionic liquids such as 1, 3-di-*n*-butylimidazolium bromide, [BBIM] Br; 1-butyl-3-methylimidazolium bromide, [BMIM]Br; 1-butyl-3-methylimidazolium tetrafluroborate, [BMIM]BF_4; 1-butyl-3-methylimidazolium hezaflurophosphate, [BMIM]PF_6 and 1-methoxyethyl-3-methylimidazolium mesylate, [MOEMIM]Ms (Yadav et al. 2010). To start with, 2 equivalent of ketone and 1 equivalent of *o*-PDA were stirred with ILs for 3-5hrs. After completion of reaction, the reaction mixture was extracted with ethyl acetate/ water and purified. The resulting 1,5-benzodiazepines was stirred with 1.1 equivalent bromosugar in ILs and the reaction mixture, extracted with DCM/water to produce1,5-benzodiazepines nucleoside (Scheme 7.9).



IL=[BBIM] Br, [BMIM] Br, [BMIM] BF_4, [BMIM] PF_6, [MOEMIM] Ms

Scheme 7.9 Plausible mechanism for the synthesis of 1,5-benzodiazepine ribofuranosides in ILs

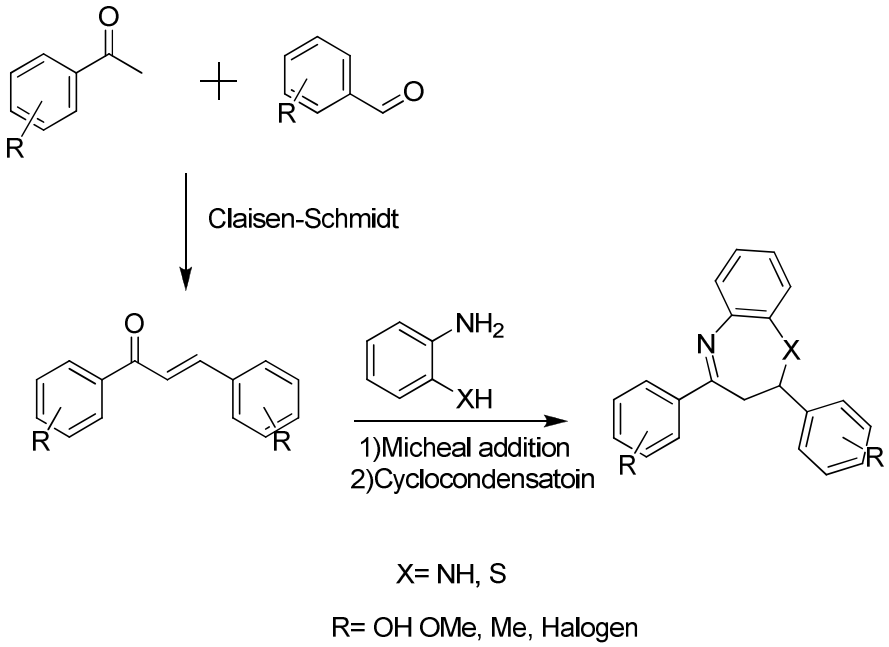
Due to the wide range of biological, industrial and synthetic applications of 1,5-benzodiazepines and 1,5-benzothiazepines, the development for a milder and more efficient method for their synthesis continues to challenge synthetic organic chemists. On the other hand, ILs, especially imidazolium salt ILs are known for their effectiveness as a catalyst/ promoter in various organic reactions like the Claisen rearrangement (Han *et al*.2005), Friedel-Crafts reaction (Surette *et al*. 1996), alkylation reaction (Koch *et al*.1976), Diels-Alder reaction (Lee *et al.*1999), asymmetric

hydrogenation (Monteiro *et al*.1997) and Heck coupling (Vallin *et al*.2002, Deshmukh et al. 2001). Although, the syntheses of 1,5-benzodiazepines based on the reaction of acyclic and cyclic ketones with *o*-PDA in ILs are well documented (Attri *et al*.2010; Jain *et al.* 2010; Xie *et al*.2009; Jadidi *et al.* 2009; Du *et al*.2006; Xu *et al*. 2005), to the best of our knowledge, the synthesis of 1,5-benzothiazepine catalysied in ILs has never been reported. Therefore, as a part of this research, we decided to examine the effect of ILs for the synthesis of 1,5- benzothiazepines based on the reaction of various chalcones with *o*-ATP.

CHAPTER 8

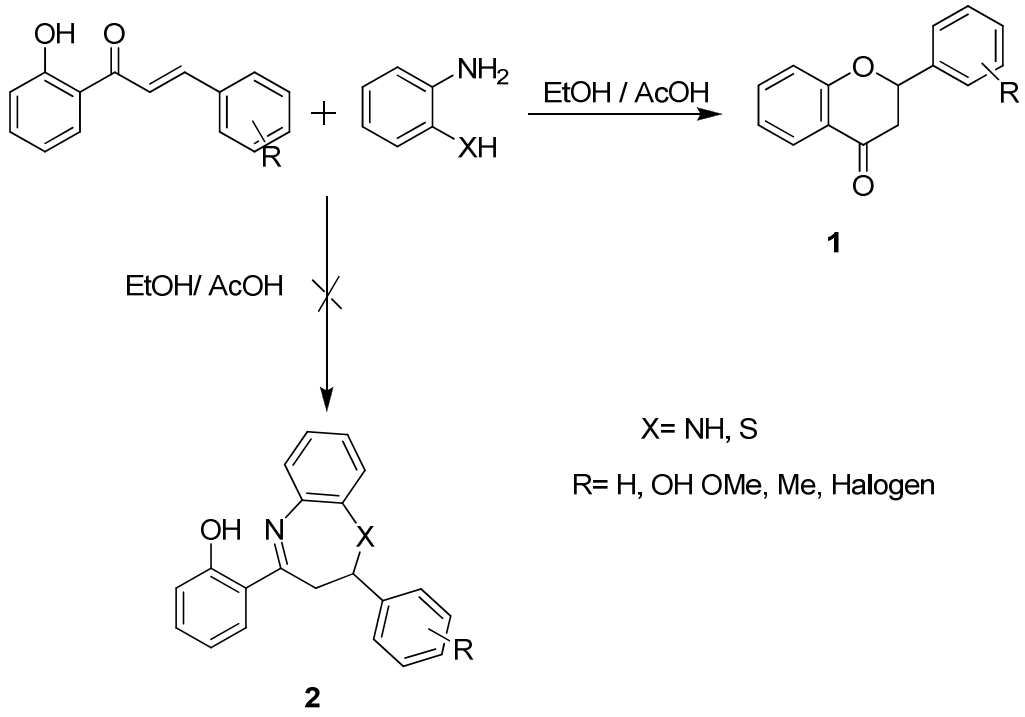
AN EFFICIENT SYNTHESIS OF 1,5-BENZOTHIAZEPINES IN IONIC LIQUIDS

The synthesis of 1,5-benzothiazepines and its other analogue 1,5-benzodiazepines generally contain three main steps (Scheme 8.1). The precursor chalcone is prepared *via* Claisen-Schmidt reaction of various benzaldehydes and acetophenones (Marais, 2005; Narender *et al*. 2007). In the second step, the chalcone will react with orthophenylendiamine (*o*-PDA) or orthoaminothiophenol (*o*-ATP) through Michael addition followed by cyclo-condensation to give the desired 1,5-benzodiazepines and 1,5- benzothiazepines, respectively.



Scheme 8.1 Synthesis of 1,5- benzodiazepines and 1,5- benzothiazepines

As mentioned in chapter 7, Reddy *et al*. and Cherkupally *et al.* reported the reaction of chalcones with *o*-PDA and *o*-ATP were expected to generate the 1,5-benzodiazepines and 1,5- benzothiazepines. However, in our hands, the reaction of 2′-hydroxchalcones with *o*-PDA and *o*-ATP in ethanol with catalytic amount of acetic acid led to the formation of flavanone, **1**, instead of the desired 1,5- benzodiazepines and 1,5- benzothiazepines, **2** (Scheme 8.2).



Scheme 8.2 Reaction of 2′-hydroxchalcones with *o*-PDA and *o*-ATP in EtOH / AcOH

This is confirmed by the spectroscopy profile of the products where for example, in the case of product **1**, when R = H, the ^{1}HNMR spectrum shows the presence of three aliphatic protons as three sets of dd at δ 5.41, 3.02 and 2.82 ppm. In addition, the presence of a carbonyl at δ 191.99 ppm in the^{13}CNMR spectra has confirmed the product to be **1** (see Appendix **A**, spectral data for flavanones).

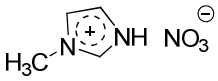
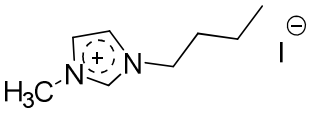
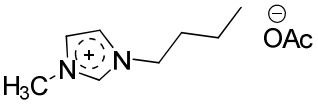
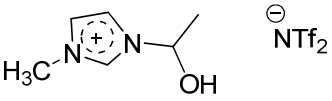
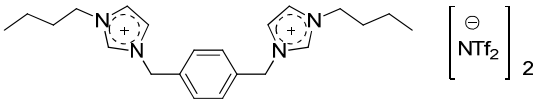
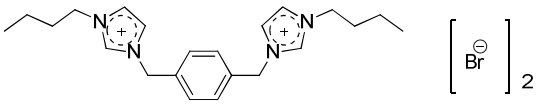
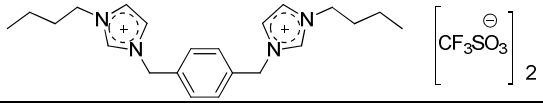
Ionic liquids (ILs), particularly imidazolium salts ionic liquids, have been classified as efficient to conventional organic solvents (D'Anna *et al*. 2009). They are reported to be environmentally friendly, thermally stable, non- volatile and reusable. ILs have been widely used as catalyst/solvent in many different reactions such as isomerization reaction, Claisen rearrangement (Han *et al*.2005), Friedel-Crafts reaction (Surette *et al*. 1996), alkylation reaction (Koch *et al*.1976), Diels-Alder reaction (Lee *et al.*1999), asymmetric hydrogenation (Monteiro et al.1997) and Heck coupling (Vallin *et al*.2002, Deshmukh et al. 2001). In some cases, the special properties of ILs have influenced the rate of chemical reactions such as in elimination reactions where, the rate of the reaction in ILs was observed to be faster than those carried out in conventional organic solvents (D'Anna *et al*.2006).

Multifunctional ILs, especially dicationic ILs have been reported to have a greater range of physical properties than most traditional, singly charged ILs. They are often more stable thermally, with lower volatility and are more flexible in tuning their physicochemical attributes (Anderson *et* al.2005; Payagala et al.2007).

The syntheses of 1,5-benzodiazepines based on the reaction of acyclic and cyclic ketones with *o*-PDA in ILs are well documented (Attri *et al*.2010; Jain *et al.* 2010; Xie *et al*.2009; Jadidi *et al.* 2009; Du *et al*.2006; Xu *et al*. 2005). However, the synthesis of 1,5-benzothiazepine in ILs has never been reported. Hence, in this project, we examined the effect of ILs for the synthesis of 1,5- benzothiazepines based on the reaction of various chalcones with *o*-ATP. The efficiency of different groups of ILs, *i.e.* mono and dicationic imidazolium ionic liquids for the synthesis of 1,5-benzothiazepine was explored.

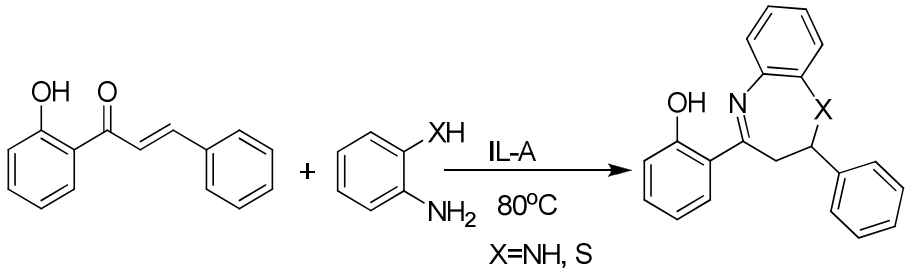
Ionic liquids (ILs) contain four monocationic ILs (IL-A to IL-D), and three dicationic ILs (IL-E to IL-G). The structures of ILs used in this work are shown in Table 8.1. Amongst these ILs, IL-B, C and D are commercially available. IL-A, E, F and G have been synthesized using reported methods (Mehdi *et al*.2007; Ganesan *et al*.2008). To investigate the effect of acidity of the media on these syntheses, the influence of various counter ions on the catalytic properties of ILs were tested. Among monocationic ILs, IL-C with acetate as counter ion, expected to has the least acidity while IL-B, and IL-D expected to be more acidic and among dicationic ILs, IL-F with two bromides as counter ions expected to be less acidic than IL-E and IL-G with triflamide and triflate respectively.

Table 8.1 Mono and dicationic imidazolium Ionic Liquids (ILs)

Entry	Ionic liquid	Structure
1	IL-A	
2	IL-B	
3	IL-C	
4	IL-D	
5	IL-E	
6	IL-F	
7	IL-G	

The main aim of this investigation was to explore the efficiency of ILs as promoter / media for the synthesis of 1,5-benzothiazepines. However, with the purpose of generalizing the method, the reaction of chalcone with *o*-PDA was also carried out. Amongst all the ILs listed in Table 8.1, IL-A is relatively cheap and easy to prepare. In addition, it can dissolve the starting materials easily. To begin with, 2′-hydroxychalcone was chosen as a model substrate to react with *o*-ATP in IL-A. To examine the capability of this media, the synthesis of 1,5-benzodiazepines also have been carried out *via* the reaction of *o*-PDA with 2′-hydroxychalcone. IL-A found to work best in equimolar quantity with respect to *o*-PDA and the chalcone whereas, in the case of *o*-ATP, excess amount of the reagent was needed for the reaction to occur (Micheli *et al*, 2001). Other parameters such as temperatures and reaction time were also studied to determine its optimum condition (Table 8.2).The best condition leading to the highest yield was obtained when the reaction mixture stirred for 120 minute at 80^0C.

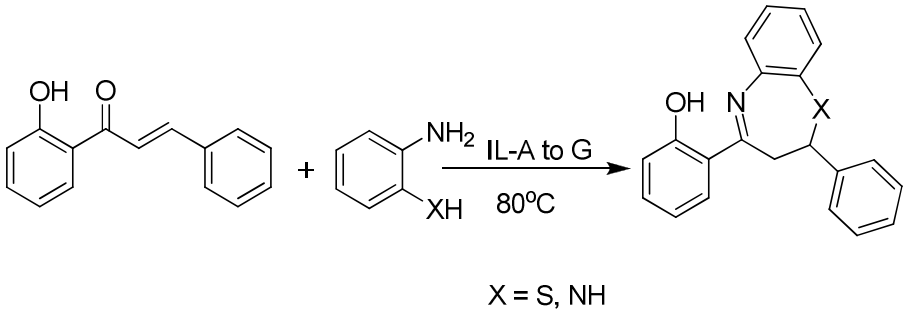
Table 8.2 Screening of the reaction conditions in IL-A



Ratio	Time (Yield)			
	30 °C	70 °C	80 °C	90 °C
1:1:1 IL-A:Chalcone:*o*-PDA	30 min (-) 60 min (-) 90 min (-) 120 min (-)	30 min (-) 60 min (10%) 90 min (27%) 120min(30%)	30 min (-) 60 min (16%) 90 min (32%) **120**min(**35**%)	30 min (-) 60min (16%) 90min (30%) 120min (35%)
1:1:1.2 IL-A:Chalcone:*o*-ATP	30 min (-) 60 min (-) 90 min (8%) 120min(12%)	30 min (2%) 60 min (30%) 90 min (62%) 120min(72%)	30 min (5%) 60 min (45%) 90 min (70%) **120**min(**75**%)	30 min (5%) 60min (45%) 90min (72%) 120min(75%)

Subsequently, 2′-hydroxychalcone was selected for further investigations to react with *o*-ATP and *o*-PDA in IL-A to IL-G (Table 8.3).

Table 8.3 The reaction between 2′-hydroxychalcone and *o*-ATP /*o*-PDA in IL-A to IL-G



X = S, NH

Entry	Ionic liquids	Reaction time(min)	Yield of benzothiazepine[a,b] (%)	Yield of benzodiazepine[a,b]
1	IL-A[c]	120	75%	35%
2	IL-B	120	78%	35%
3	IL-C	120	70%	30%
4	IL-D	100	78%	30%
5	IL-E	100	87%	35%
6	IL-F	100	82%	30%
7	IL-G	80	92%	40%

[a] Yield of isolated product

[b] The product was characterized by ^{1}H NMR and mass spectral data was identical with the literature

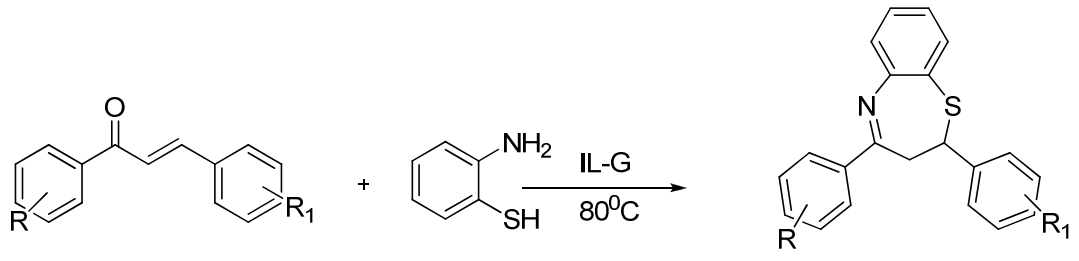
[c] Our collaborators reported the same reaction in 95% yield / 60 min for 1,5- benzothiazepine

All ILs seemed to promote the synthesis of 1,5- benzothiazepine selectively, where the yield of reaction between *o*-ATP and, 2′-hydroxychalcone was observed to be good to excellent in all cases (75-90%). However, reaction between the same chalcone with *o*-PDA gave lower yields (30-35%). Presumably, this low yield is due to the lower reactivity of *o*-PDA compare to *o*-ATP.

The counter ion was observed to influence the reaction time as well as yield of the reaction. This observation could be explained by effect of the counter ion on the acidity of ILs (Du *et al*. 2006).Among the monocationic ILs (IL-A to IL-D), the lowest yield of 1,5-benzothiazepine formed was obtained when the reaction was carried out in

IL-C. However, when IL-B was used as the media for the reaction, the yield obtained was better at 78%.The difference between IL-C and IL-B lies in their counter ion. Acetate was the counter ion for IL-C while iodide was the counter ion for IL-B. Reaction in IL-D, with triflamide as the counter ion performed better than both reactions in IL-B and IL-C giving the same yield as product as IL-B (78%) but in shorter reaction time. Amongst the geminal dicationic ILs (IL-E to IL-G), triflamide, bromide and triflate counter ions were found also to affect on the reaction time and yield differently. In this case, IL-G was observed to be the most efficient media for the reaction of *o*-ATP with 2′-hydroxychalcone wherein a shorter reaction time and higher yield of desired product was observed. Based on this observation, the IL-G was used to further explore the efficiency of the media for the synthesis of various 1,5-benzothiazapines using different chalcones (Yeaghoobi *et al*., 2012; unpublished result).

Variety of 1,5-benzothizepines were successfully synthesized using this geminal dicationic IL (Scheme 8.3).

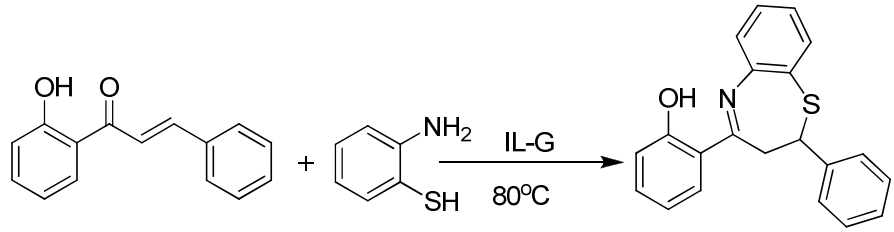


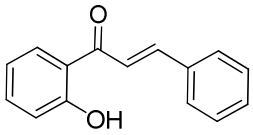
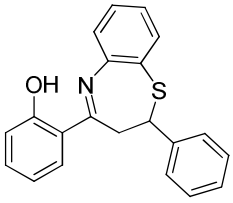
Scheme 8.3 Synthesis of 1,5-benzothiazepines in IL-G

In all the reactions carried out, the ionic liquid seemed to act not only as the medium but also a promoter for the reaction in relatively shorter reaction times were achieved to those reported when using the conventional medium (80-120 min). For example, the synthesis of 1,5-benzothiazepines in $Ga(OTf)_3$ / acetonitrile was reported to take in more than 8 hrs to complete (Pan *et al*. 2008). However, in all reaction conditions the amount of products obtained was also observed to be good, in most cases ranging between 75% to 90% yields with an easy work up.

The reusability of a catalyst is important from the environmental and economic point of view. The reusability of these ionic liquids was therefore examined using sequential reactions. The results indicated that ILs could be recovered and reused successfully for several times without remarkable decrease in its activity. As shown in Table 8.4, the recovered IL did not show appreciable loss in its activity since more than 83% yield of the 1,5-benzothiazepine was obtained even when the IL was reused for the third time (Table 8.4).

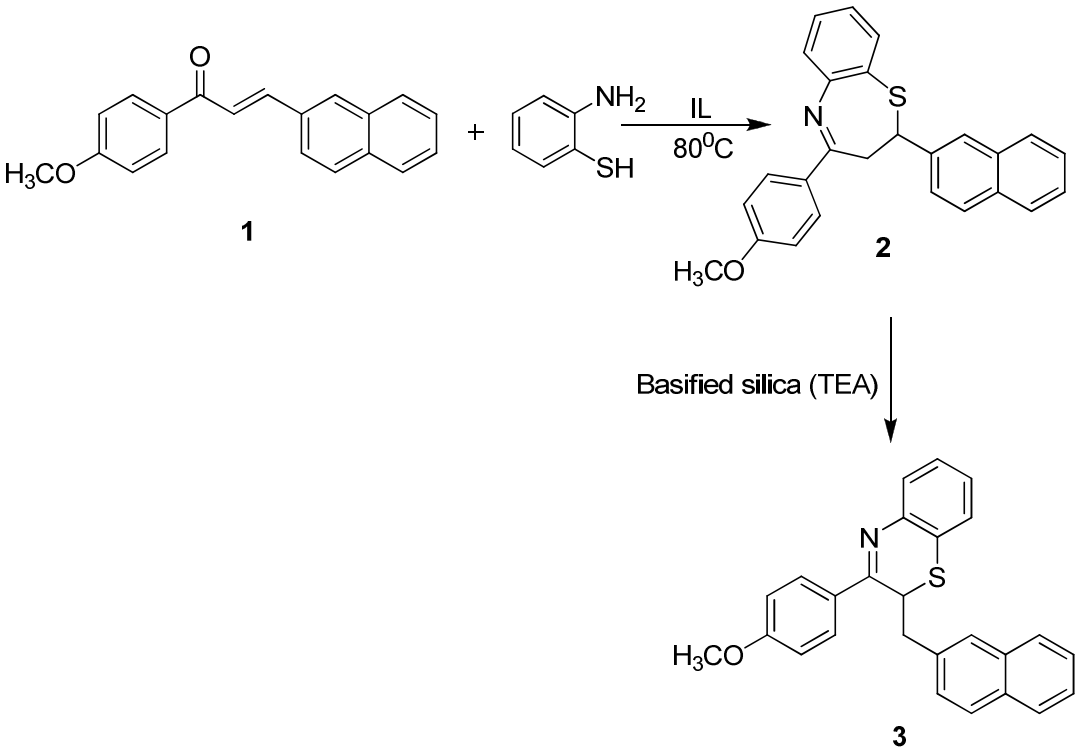
Table 8.4 The reaction between *o*-ATP and 2′-hydroxychalcone in IL-G media and the ionic liquid recycling



Substrate	Product	Condition	[a]Yield
		1 equimolarIL, 80^0C 80min	97%
		1^{st} recycle, 80^0C 80min	89%
		2^{nd}recycle, 80^0C 80min	83%

[a]Isolated yield calculated from 2′-hydroxychalcone

As expected, the reaction between chalcone, **1**, with *o*-ATP in IL produced 1,5-benzothiazepne, **2**. Formation of compound **2** was observed in ^{1}HNMR data (crude mixture of the reaction). In order to obtain pure 1,5-benzothiazepne, **2**, the crude mixture was passed through a basified silica column. Surprisingly, a six membered ring thiazine, **3**, was obtained as the product (Scheme 8.4). The six membered ring thiazine, **3**, resultes from ring contraction of the seven membered ring thiazepine, **2**, shown in Scheme 8.4. The ^{1}HNMR profile of three aliphatic protons for compounds **2,** and **3**, is shown in Figure 8.3 (Loghmani & Yaeghoobi, *et al*., 2012; unpublished result).



Scheme 8.4 Transformation of thiazepine to thiazine

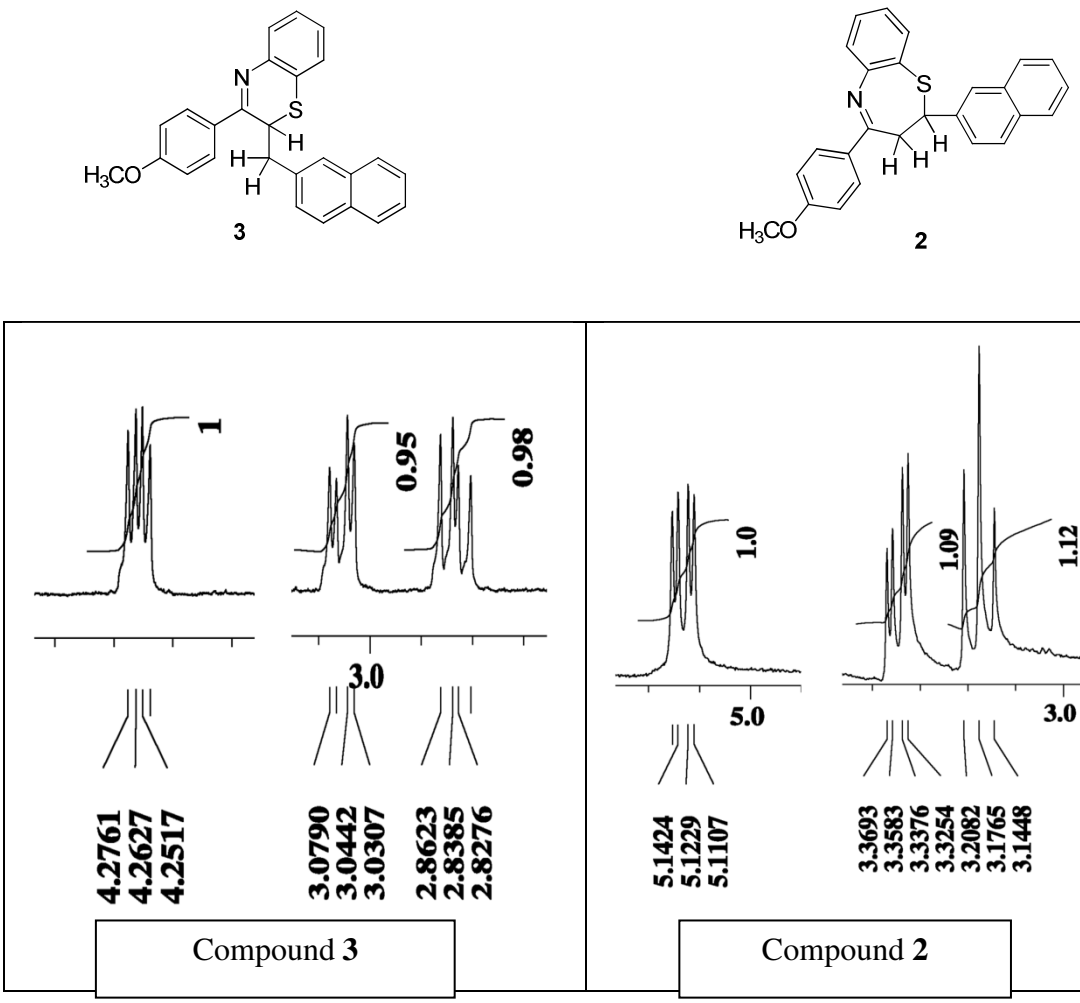


Figure 8.1 Comparison ^{1}H NMR of spin-spin coupling between CH and CH_2 of the compounds **2** (right) and **3** (left)

This ring rearrangement caused an up field shift in all signals belonging to aliphatic protons of the thiazepine ring. In addition, due to this ring contraction, the splitting profile of these protons was also affected. In compound **2**, a triplet at δ 3.17 ppm, a dd at δ 3.34 ppm, and a dd at δ 5.12 ppm was observed while in compound **3**, three sets of dd at δ 2.82 ppm, δ 3.05 ppm and at δ 4.25 ppm was observed (Figure 8.1). Interestingly, in the ^{13}C NMR spectrum, the aliphatic carbon of compound **2** appeared at δ 60.66 ppm while aliphatic carbon of compound **3** was observed at δ 35.78 ppm. This significant up field shift is may be attributed to the distance of this carbon from imine

group in six membered ring.Finally, compounds **2** and **3** were recrystalized from ethyl acetate. The crystal structure of compounds **2** and **3** are shown in Figures 8.2 and 8.3.

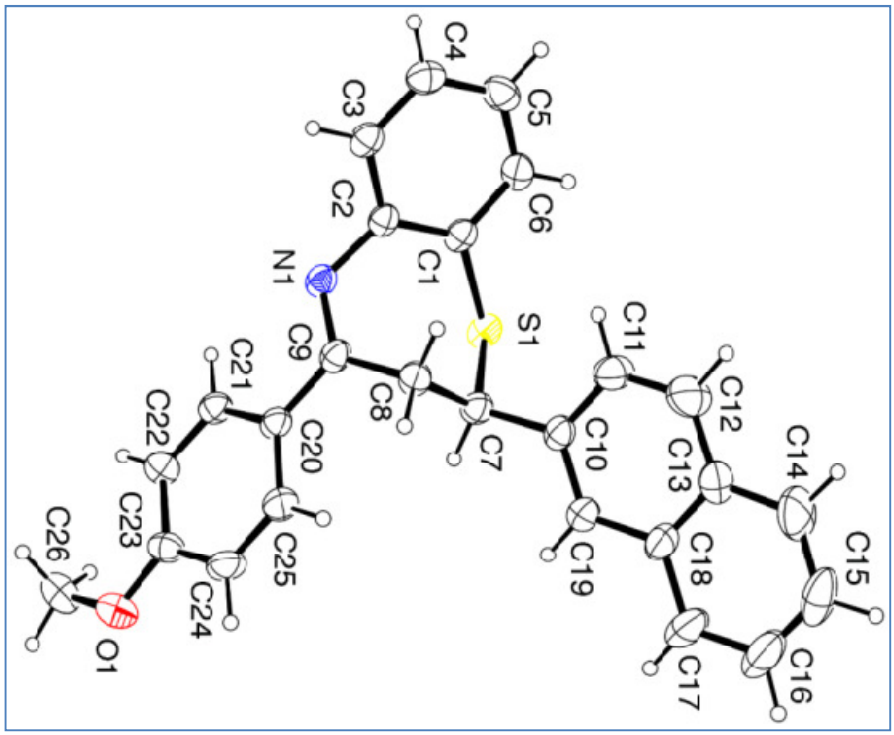


Figure 8.2 X-ray crystal structure of 4-(4-methoxyphenyl0-2-(naphthalene-2-yl)-2, 3-dihydrobenzo [*b*][1,4]thiazepne with thermal ellipsoids at 50% probability. Atoms are labeled anonymously. Crystallographic data can be referred from appendix C.

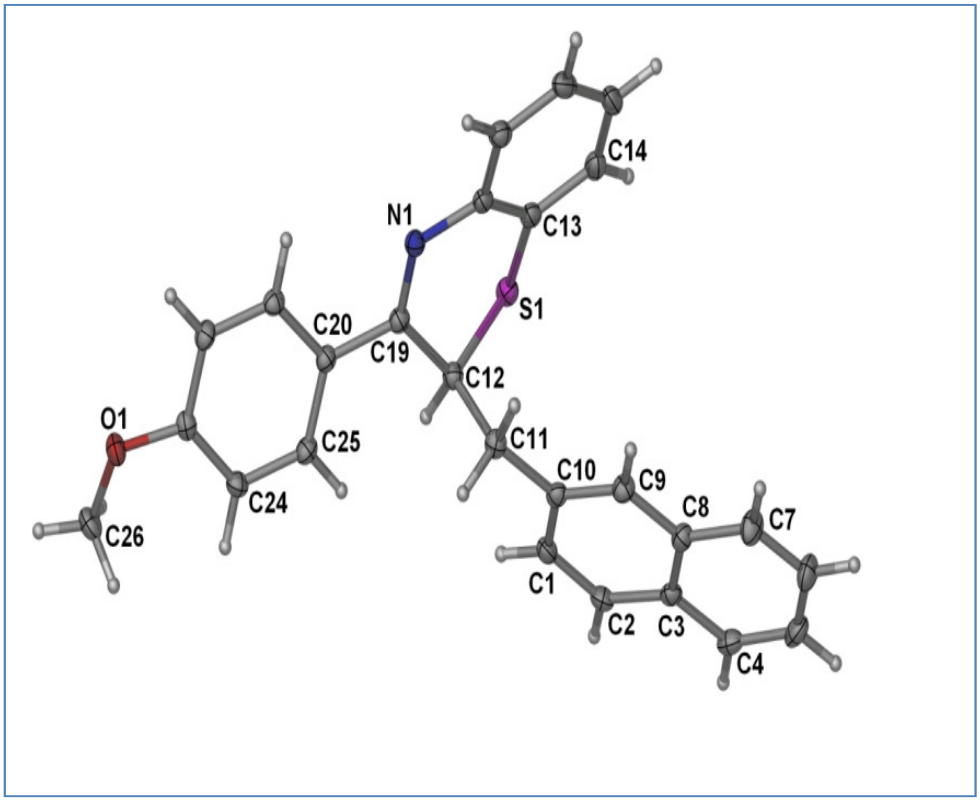
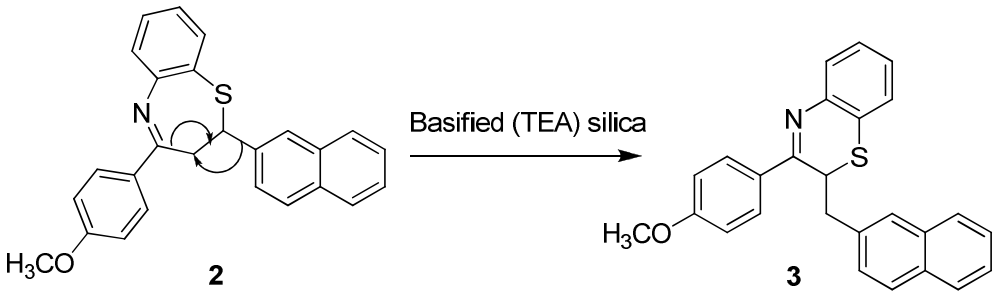


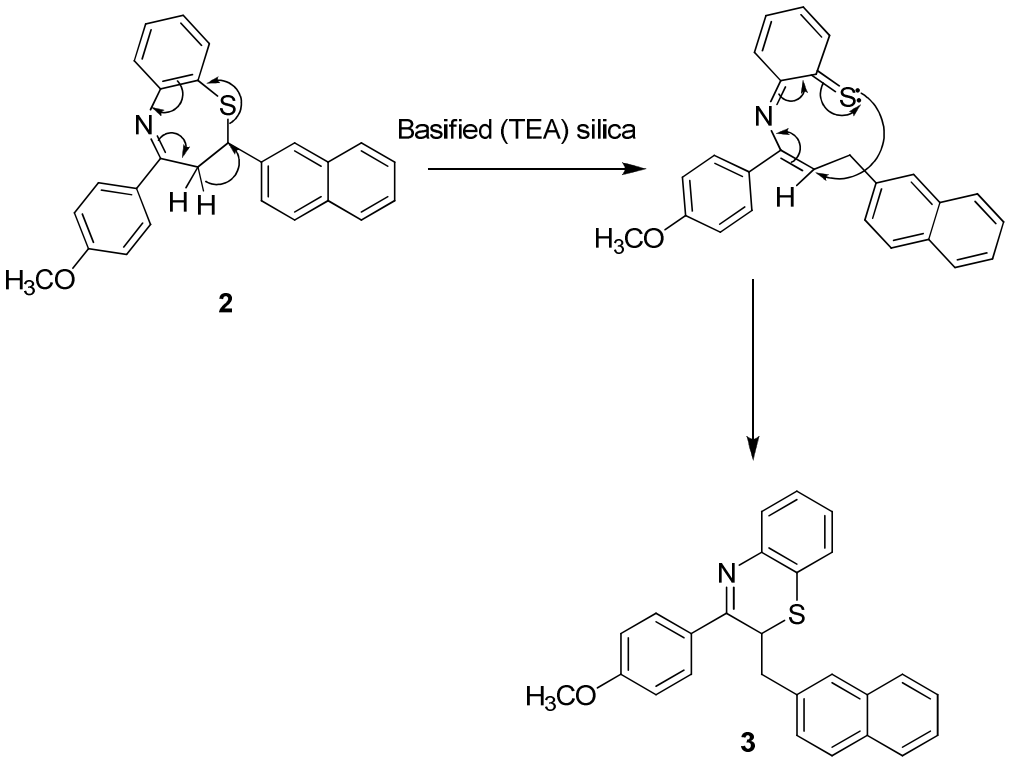
Figure 8.3 X-ray crystal structure of 3-(4-methoxyphenyl0-2-(naphthalene-2-ylmethyl)-2hydrobenzo [*b*][1,4]thiazine with thermal ellipsoids at 50% probability. Atoms are labeled anonymously. Crystallographic data can be referred from appendix C.

There are two possible mechanistic interpretations for this transformation. The first possibility is demonstrated in Scheme 8.5 in which the compound **2** is converted to compound **3** through a naphthyl shift.



Scheme 8.5 Conversion of thiazepine, **2** to thiazine, **3** through naphthyl shift

The second plausible mechanism for this transformation is shown in Scheme 8.6 which contain hydrogen shift followed by a ring opening and finally a ring closing.



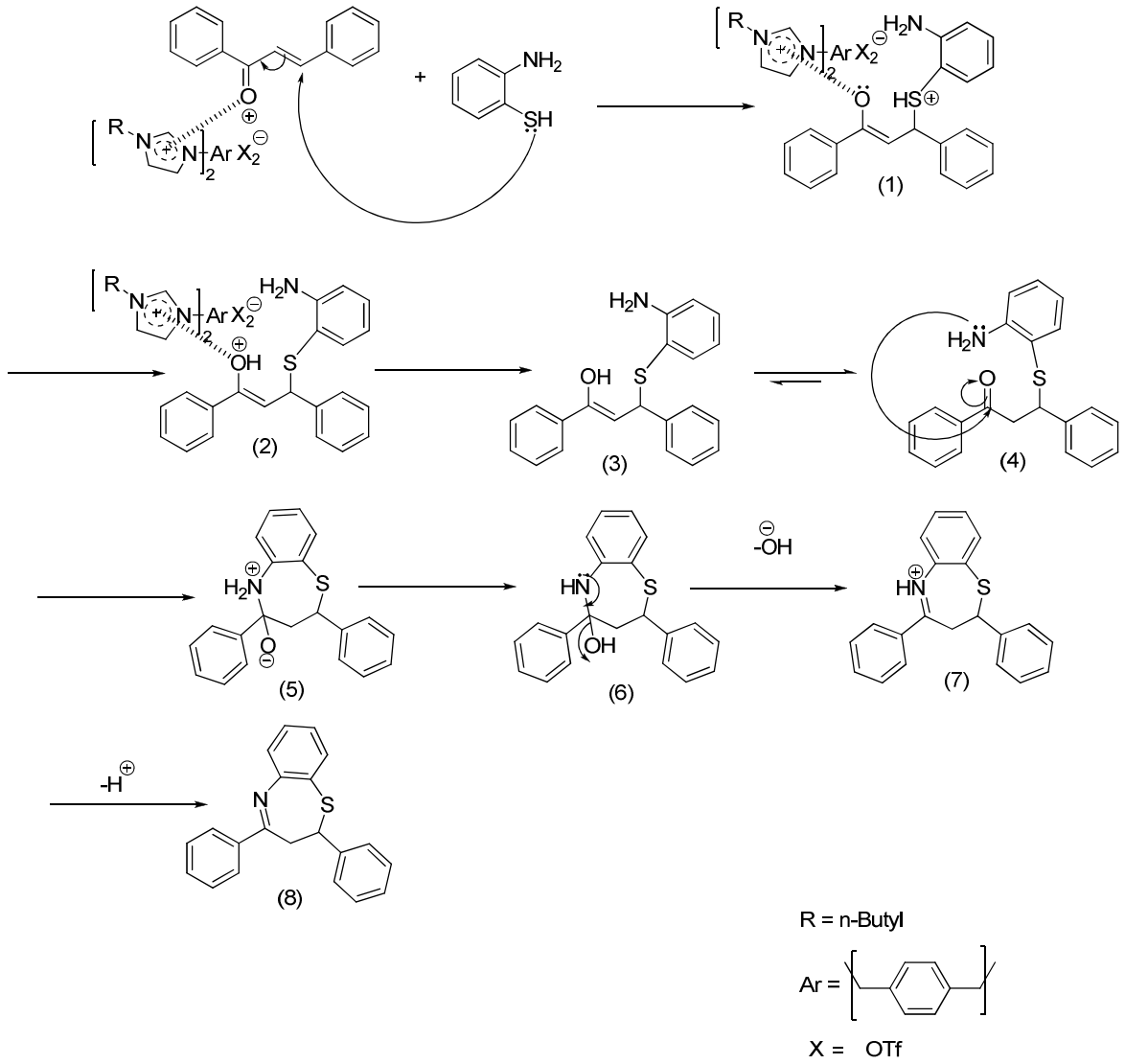
Scheme 8.6 Conversion of thiazepine, **2** to thiazine, **3** through hydrogen shift

For the formation of 1,5-benzothiazepines from chalcones and *o*-ATP, two possible mechanisms were considered. One involves the 1, 4-addition reaction followed by a cyclo-condensation reaction (Scheme 8.7, path A) while the second one is thought to go 1, 2-addition followed by cyclization reaction (Scheme 8.7, path B).

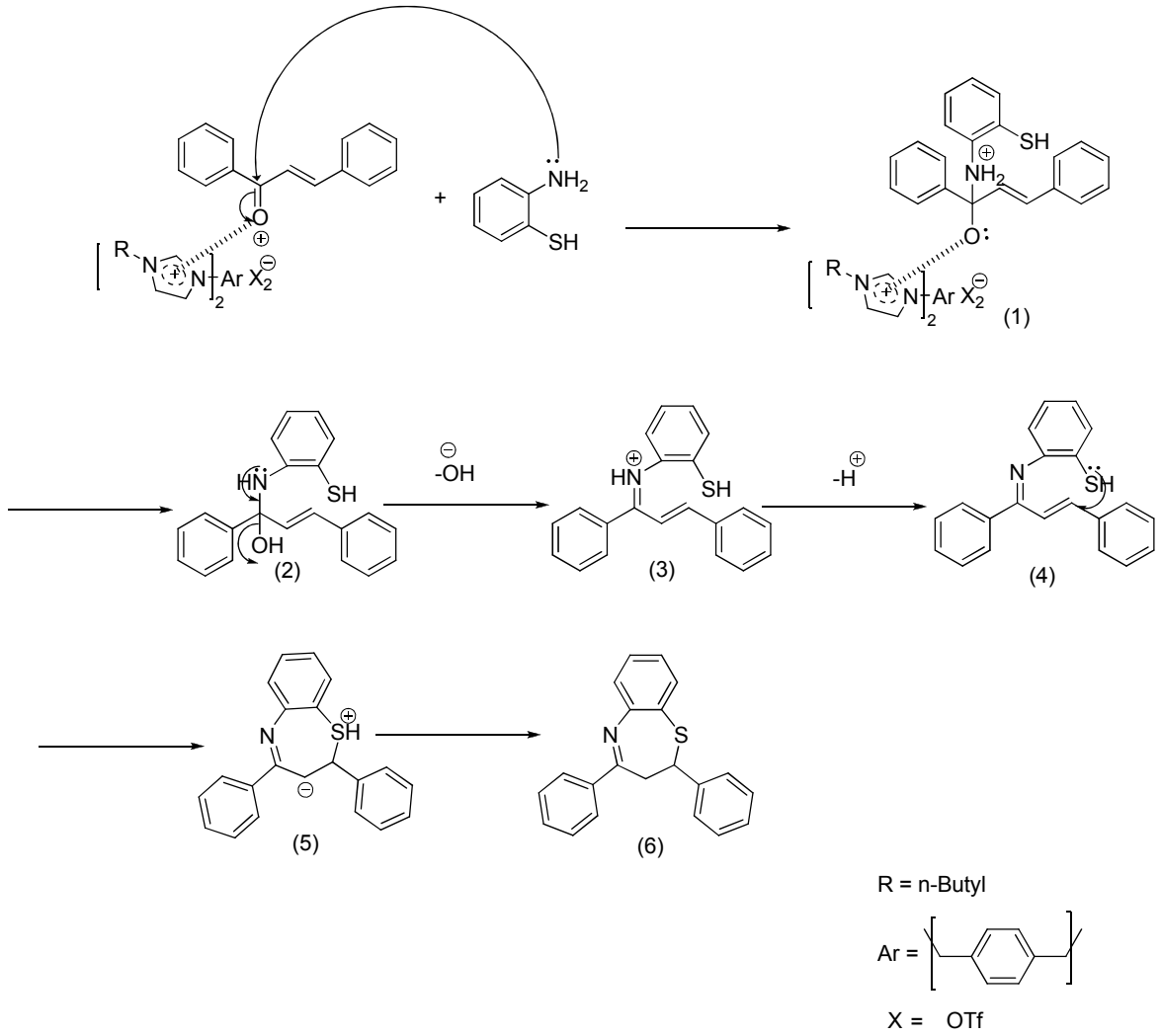
To deduce the reaction mechanism, the intermediate of the reaction between *trans*-chalcone and *o*-ATP was isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy. The NMR data clearly indicated that amongst the two possible intermediates (Scheme 8.5, (4), path A and (4), path B) ; the preferred path is A due to the presence of three key aliphatic protons in the ^{1}H NMR spectrum; i.e. at δ 3.56 (dd, *J*=6.95Hz, *J*=17.62Hz, 1H; CO-$\underline{CH_2}$- CH-S), δ 3.64 (dd, *J*=7.31Hz, *J*=17.54 Hz, 1H; CO-$\underline{CH_2}$-

CH-S), δ 4.74 (t, J = 6.73Hz, 1H; CO-CH_2- CH-S;); (Appendix B, spectral data for Michael adduct) and a carbonyl group in ^{13}C NMR spectrum at δ 197.15 which is in agreement with reported data for a Michael adduct (Katritzky *et al*.2000). IR spectra of this compound indicated the presence of NH_2 at 3352cm^{-1}. This intermediate was recrystallized from ethanol and the structure was confirmed by X-ray crystallography (Yaeghoobi *et al.* 2011). The X-ray crystal structure of this intermediate is shown in Figure 8.4. addition at the carbonyl carbon was expected to be faster since complexation of the IL to oxygen makes the carbonyl more electrophilic. However, the bulkiness of IL could reduce this side to be more hindered. The softer fourth position which presumably more exposed then is subjected to the attack by sulfur and reaction will proceed through a 1, 4 Michael addition reaction.

Path A:



Path B:



Scheme 8.7 Proposed mechanism for Synthesis of 1,5-benzothiazepines in IL-G

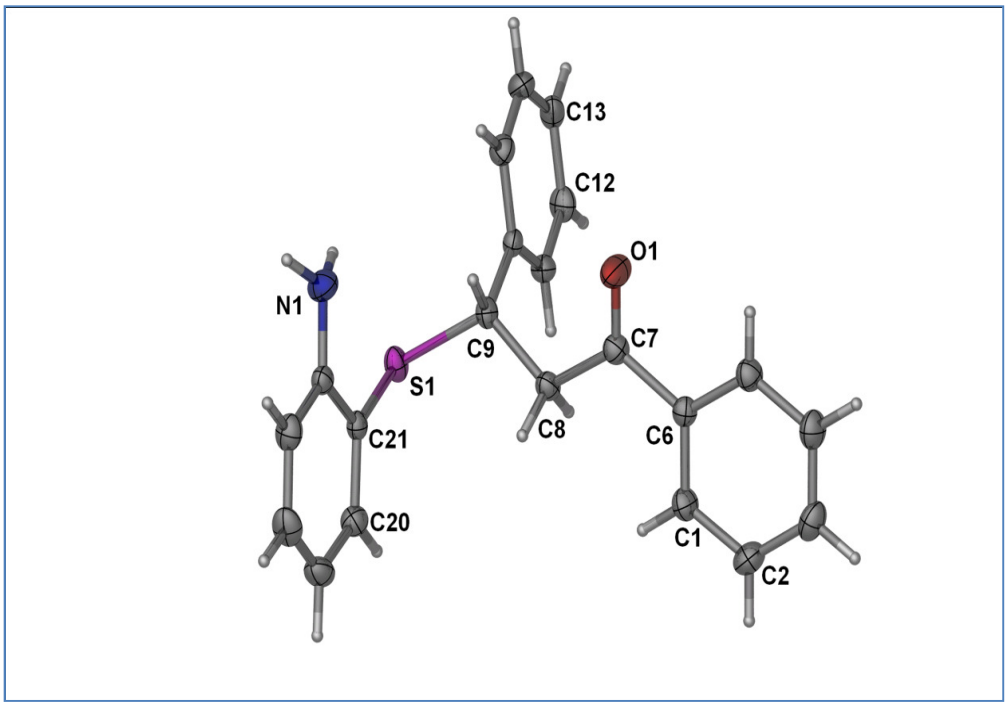


Figure 8.4 X-ray crystal structure of the intermediate (4), path A, 3-(2-aminophenylthio)-1, 3-diphenylpropan 1-one with thermal ellipsoids at 50% probability. Atoms are labeled anonymously. Crystallographic data can be referred from Appendix C.

CHAPTER 9

1,5-BENZOTHIAZEPINES WITH POTENTIAL NEURAMINIDASE INHIBITION EFFECT

As mentioned in previous chapters, 1,5-benzothiazepines have been reported to possess a wide range of biological activities such as antifeedants (Reddy *et al.* 1993), tranquilizers (Kugita *et al.* 1971), antidepressants (Geyer *et al*. 1970), CNS stimulants (Kawashima *et al.*1985), calcium channel blockers (Kugita *et al.* 1971), antimicrobial agent (Dandia et al. 1998), antibacterial and antifungal properties (Jadhav *et al*.1983; Barot *et al*. 2001; Cherkupally *et al*. 2008) and Platelet aggregation inhibitory (Bariwal *et al*. 2008). Nevertheless, previous reports on the antiviral property of 1,5-benzothiazepines were mainly concerned with its potential bioactivity against Hepatitis B and HIV-1 (Nicol *et al*. 1992; Delpa *et al*.2000; Pauwels *et al.* 1990; Grandolini *et al.*1999; Di Santo *et al*. 2005). In our continue efforts to search for a potent ihibitor for H1N1 virus, we set out to investigate 1,5-benzothiazepines as neuraminidase inhibitors of the H1N1 virus.

A library of 1,5-benzothiazepine derivatives was generated by incorporating various substituent like OH, OMe, methylenedioxy, Methyl, halogen, naphthalene, and NH_2 in various parts of the molecule. Electron-donating and electron-withdrawing groups were introduced into the basic structure of 1,5-benzothiazepines backbone, in order to study the influence of these substituents on the neuraminidase inhibition activity. Preliminary computer modeling results suggested that hydroxyl-, methoxy- and methylenedioxy-groups in the molecule could form hydrogen bonds with neuraminidase. Benzene and naphthalene rings on the other hand, could engage in π interaction with the enzyme, allowing better protein- ligand interaction. The general strategy to further explore this template is depicted in Figure 9.1. To explore the effect of different functional groups on the activity of 1,5-benzothiazepines, MA1-MA15 (Table 9.1) have been synthesized from chalcones (listed in Table 4.2) All the synthesized heterocycles have been

evaluated for their potential bioactivity as neuraminidase inhibitors (Manuscript under preparation).

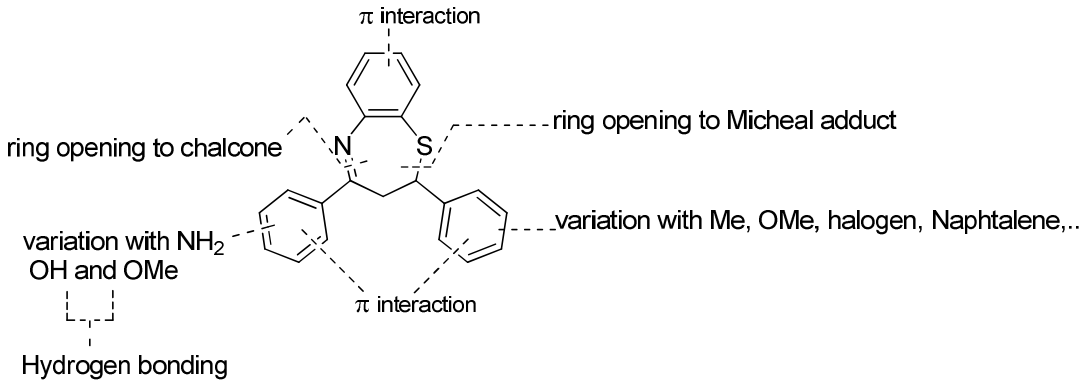
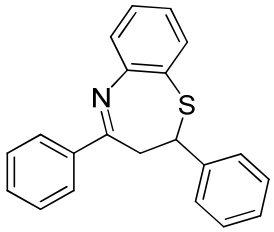
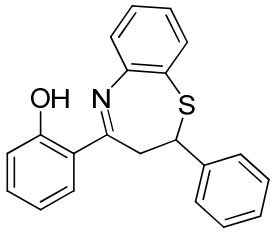
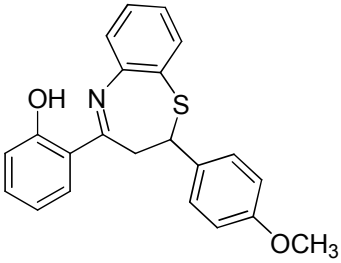
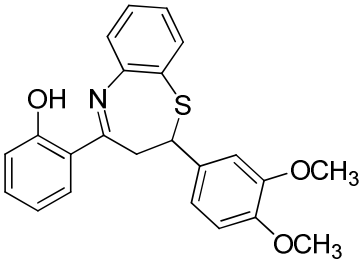
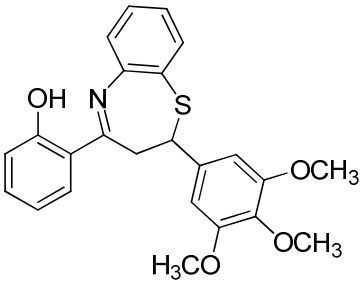
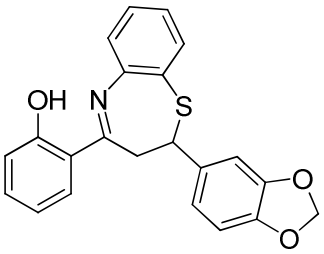
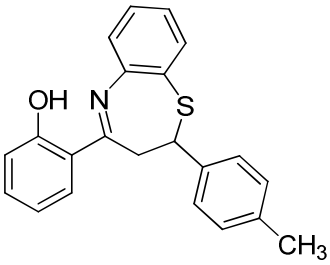
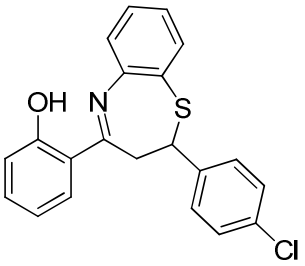
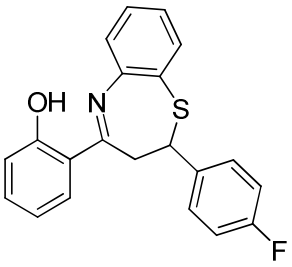
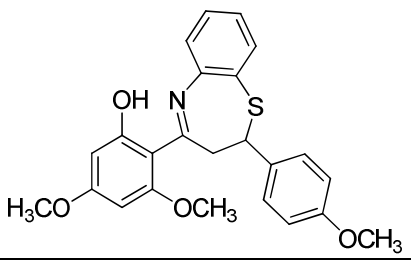


Figure 9.1. General strategy to prepare 1,5-benzothiazepines with potential H1N1inhibition effect

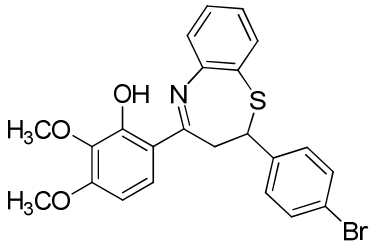
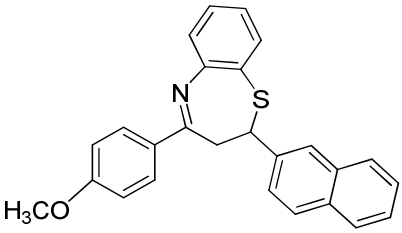
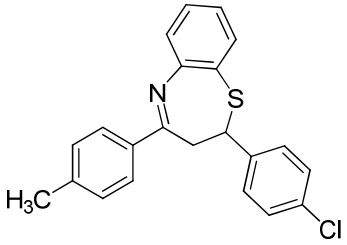
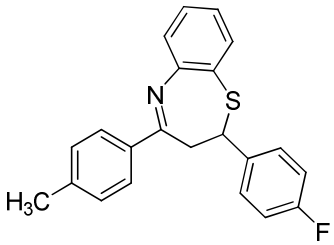
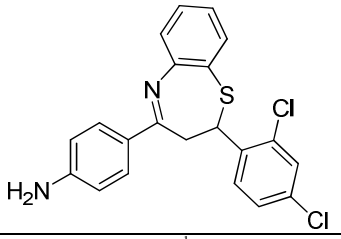
Table 9.1 Yields and melting points of 1,5-benzothiazepine synthesized

Entry	Structure	Yield[a](%)	mp(^{0}C) found	mp(^{0}C) reported
MA1		52	102	96-97
MA 2		92	151	154-155
MA 3		91	165	160-161
MA 4		83	161-162	-

'**Table 9.1**, continued'

Entry	Structure	Yield[a](%)	mp(^{0}C) found	mp(^{0}C) reported
MA 5		80	160-162	-
MA 6		75	138	142
MA 7		87	154	156
MA8		85	162	168
MA9		90	152	156
MA10		87	168-170	-

'**Table 9.1**, continued'

Entry	Structure	Yield[a](%)	mp(^{0}C) found	mp(^{0}C) reported
MA11		78	156-157	-
MA12		82	128-130	-
MA 13		73	119-121	-
MA14		75	118-119	-
MA15		70	179-181	-

[a] Products were characterized by ^{1}H NMR and mass spectral data
[b] Yields of isolated products

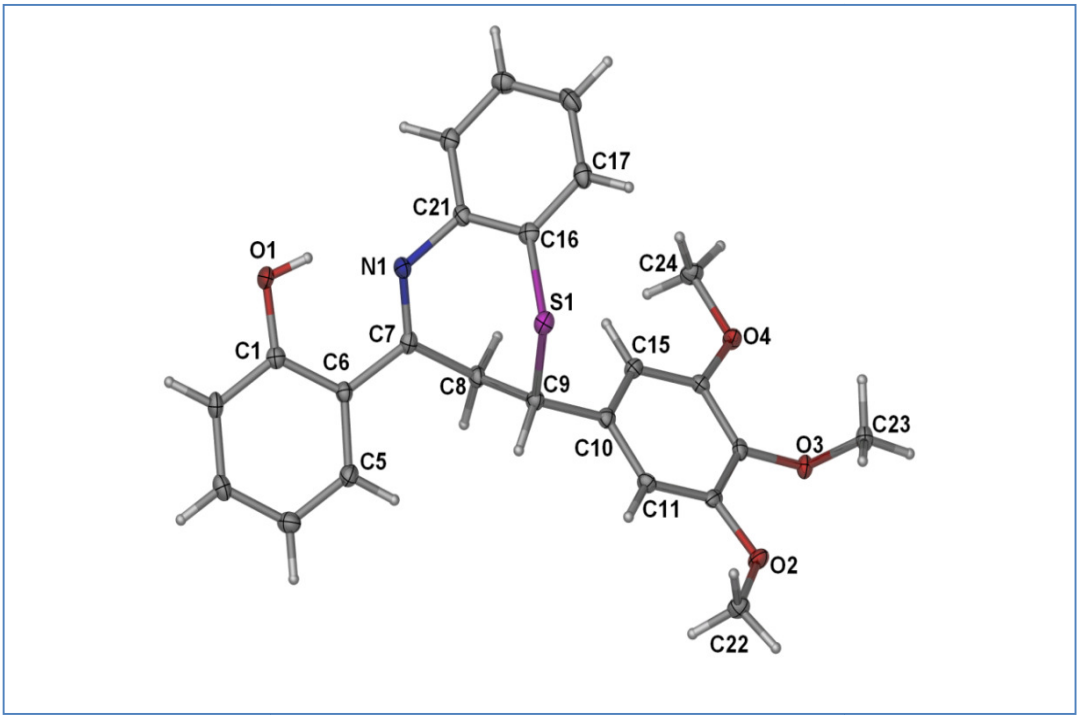


Figure 9.2. X-ray crystal structure of 2-(2-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydrobenzo[b][1, 4] thiazepin-4-yl)phenol with thermal ellipsoids at 50% probability. Atoms are labeled anonymously. Crystallographic data can be referred from appendix C.

1,5-benzothiazepines MA1-MA15 were docked to the neuraminidase of A/ Breving Mission/ 1/1918 H1N1 strain in complex with zanamivir (PDB ID = 3B7E, obtained from protein data bank, http://www.pdb.org). To evaluate these compounds for their potential H1N1 activity, the azepines were tested against neuraminidase. The result of bioassay (percentage of the inhibition in **250**µm) and Cdocker energy is summarized in Tables 9.3. Compounds MA4, MA7, MA8, MA10, MA11 and MA12 with promising Cdocker energy (compared to DANA with Cdocker interaction energy equal to -46.11 kcal/mol), were expected to be very active against the neuraminidase. Unfortunately, the bioassay result did not corroborate the calculation obtained where these compounds showed poor activity against neuraminidase. The poor activity of 1,5-benzothiazepines against H1N1 is could be due to the size of the seven membered ring,

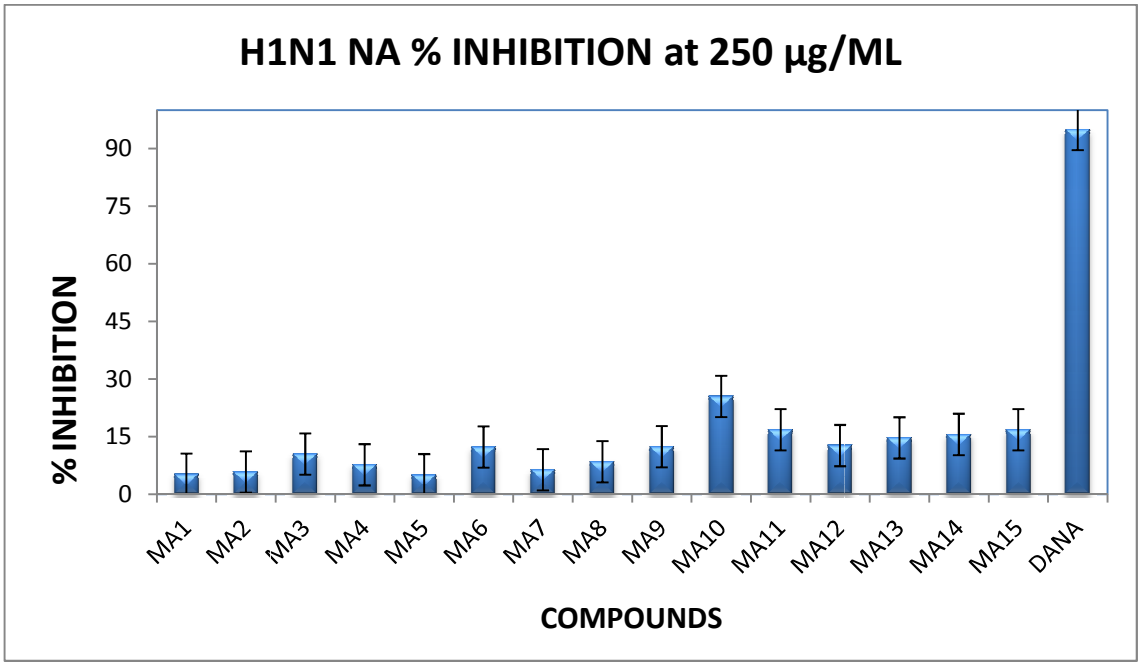
lack of flexibility and solubility of these compounds. This observation might be also due to the binding of azepines as ligand to the allosteric site rather than the active sites (Ryu *et al.* 2008).

Table 9.2 1,5-benzothiazepines activity against Neuraminidase

Entry	(-) Cdocker interaction energy[a,b] (kcal/mol)	Inhibition in **250**µm (%)[c]
MA1	29.26	5.2
MA2	27.82	5.8
MA3	32.81	10.5
MA4	40.52	7.7
MA5	28.85	5.1
MA6	28.75	12.3
MA7	32.86	6.4
MA8	35.34	8.5
MA9	25.63	12.4
MA10	34.31	25.5
MA11	36.23	16.8
MA12	39.08	12.7
MA13	23.50	14.7
MA14	29.75	15.6
MA15	23.26	16.8

a Calculation performed by **Frimayanti** *et al.*using Cdocker (Discovery Studio 2.5, Accelrys) ;
b Enzym: 3b7E (Neuraminidase of A/ Breving Mission/ 1/1918 H1N1 strain in complex with zanamivir;.
c bioassay erformed by **Ikram** *et al.* using DANA as standard with -46.11 kcal/molCdocker interaction energy

Table 9.3.Bioassay results of 1,5-benzothiazepines



CHAPTER 10

CONCLUSION

In conclusion, up to almost one hundred flavonoids and 1,5- benzothiazepines have been synthesised from well-established routes as well as newly developed one-pot synthetic method.

The environmentally benign one-pot method using PMA/SiO_2 in ethanol has successfully been applied toward the preparation of flavanone analogues in reasonable yields. The synthesized flavonoids (chalcones and flavanones) were investigated for their potency as NA inhibitors.

The mono and dicationic ILs were employed as reusable catalyst to synthesize 1,5-benzothiazepines in reasonable quantities. The synthesized compounds were investigated for their possible NA inhibitory activity.

Chalcones are shown to be fairly active as NA inhibitors while flavanones, even with the promising calclulation results of Cdocker energy (compared to DANA with Cdocker interaction energy equal to -46.11 kcal/mol), were observed to be not active against neuramidase. This observation was due to the flavanones binding at the allosteric sites rather than the active sites. In addition, quantitative structure-activity relationships for the chalcone compounds with the aid of 2D and 3D-QSAR models have been also studied.

1,5-benzothiazepines, with promising Cdocker energy (compared to DANA with Cdocker interaction energy equal to -46.11 kcal/mol), were expected to be active against neuraminidase. Unfortunately, the bioassay result did not corroborate the

modeling results. The poor activity of 1,5-benzothiazepines against H1N1 could be due to the larger size of the seven membered ring, lack of flexibility and solubility.

Further studies are underway to synthesize other chalcone-based and non chalcone-based heterocyclic compounds with potential bioactivities. Moreover, enantioselective synthesis of these flavanone, 1,5-benzothiazepines and other heterocyclic systems, could be carried out to enable investigation on the effect of enantio purity on the bioactivity of these compounds.

CHAPTER 11

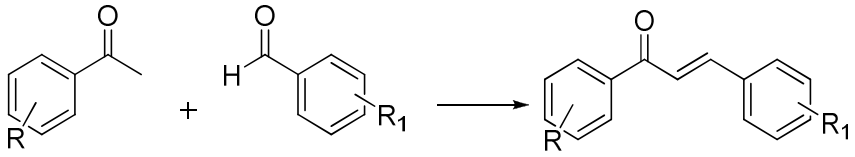
EXPERIMENTAL SECTION

Experimental procedure and spectroscopy data for chapter 4 and 5:

General

All melting points were determined using a Mel-Temp II melting point instrument. NMR spectra were obtained using a Jeol ECA 400 (400 MHz) and Lambda 400 NMR spectrometers with TMS as the internal standard. All chemical shifts are reported in ppm. The IR spectra were taken with a Perkin Elmer 400 ATR-FTIR spectrophotometer. The mass spectra were taken on an Agilent 1200 LC/MS, analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60 F-254) using UV light (254 and 366 nm) for detection. Column chromatography was carried out with silica gel 60 (230-400 mesh) from Merck. All target compounds were characterized by ^{1}H, ^{13}C and other spectroscopy analyses. All reactions were carried out under nitrogen atmosphere unless specified. All solvents and reagents were purchased from Aldrich, Merck or Fisher.

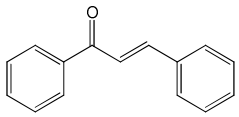
General procedure for preparation of Chalcone MC1- MC50:



R, R_1= OH, Me, OMe, Halogen,...

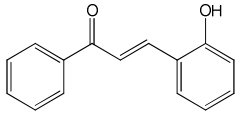
The substituted chalcones MC1-MC50 were prepared *via* standard Claisen-Schmidt reaction. To a solution of various acetophenones (1 eq) in Ethanol (AR grade) (2.5mL/mmol), Sodium hydroxide (3 eq) was added. After10 min, appropriated benzaldehydes (1.2eq) were added and the solutions were stirred at room temperature overnight. After cooling the reaction mixtures with ice, the mixture was neutralized carefully using 1N hydrochloric acid. The crude mixture was extracted with ethyl acetate, washed with water and brine afforded chalcones MC1-MC50 which were purified by column chromatography using hexane: ethyl acetate as eluent to give pure chalcones (32%-92%); except MC46-MC50 which directly utilized for synthesis of flavanones.

1, 3-Diphenyl-2-propen-1-one (*E*-chalcone) MC1



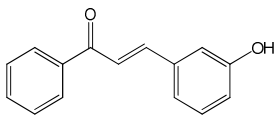
Pale yellow solid; Mp = 55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-8.03 (m, 2H), 7.81 (d, *J*= 15.98Hz, 1H), 763-7.65 (m, 2H), 7.55-7.60 (m, 2H), 7.48-7.52 (m, 2H), 7.39-7.42 (m, 3H);^{13}C NMR (400 MHz, $CDCl_3$): δ 190.52, 144.81, 138.16, 134.83, 132.76, 130.52, 128.93, 128.59, 128.47, 128.41, 122.02.

(*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one MC2



Light green solid; Mp = 149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J*= 16.05 Hz, 1H), 7.97 (d, *J*= 6.93Hz, 2H), 765 (d, *J*= 16.05Hz, 1H), 7.51 (t, *J*= 8.75Hz, 2H), 7.43 (t, *J*= 8.39Hz, 2H), 7.23 (d, *J*= 8.02Hz, 1H), 6.89 (t, *J*= 8.02Hz, 1H), 6.84 (d, *J*= 8.39Hz, 1H), 6.31 (bs, OH);^{13}C NMR (400 MHz, $CDCl_3$): δ 191.07, 155.62, 140.63, 138.36, 132.48, 131.81, 129.68, 128.68, 123.00, 122.34, 121.11, 116.63.

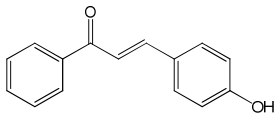
(*E*)-3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one MC3



Yellow solid; Mp = 152°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01(d, *J*= 7.80Hz, 2H), 7.76 (d, *J*= 15.61Hz, 1H), 7.58-7.61 (m, 1H), 7.51 (t, *J*= 7.80Hz, 3H), 7.30 (t, *J*=

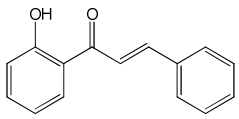
7.80Hz, 1H), 7.22 (d, *J*= 8.30Hz, 1H), 7.14 (s, 1H), 6.90-6.92 (m, 1H), 5.27 (bs, OH);^{13}C NMR (400 MHz, $CDCl_3$): δ 190.86, 155.98, 144.71, 138.08, 136.53, 133.02, 130.28, 128.76, 128.63, 122.49, 121.27, 117.82, 114.97.

(*E*)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one MC4



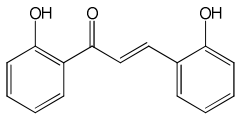
Yellow solid; Mp = 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00(d, *J*= 7.08Hz, 2H), 7.78 (d, *J*= 15.45Hz, 1H), 7.55-7.59 (m, 3H), 7.50 (t, *J*= 7.72Hz, 2H), 7.41 (d, *J*= 15.45Hz, 1H), 6.89 (d, *J*= 8.36HZ, 2H), 5.62 (bs, OH);^{13}C NMR (400 MHz, $CDCl_3$): δ 191.06, 158.20, 145.04, 138.99, 132.78, 130.66, 128.70, 128.55, 127,74, 119.83, 116.10.

(*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one MC5



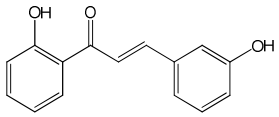
Yellow solid; Mp = 89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.86 (s, OH), 7.81-7.90(m, 2H), 7.61-7.64 (m, 3H), 7.35-7.49 (m, 4H), 7.02 (d, *J*= 8.80HZ, 1H), 6.92 (t, *J*= 8.21HZ,1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.83, 163.69, 145.57, 136.52, 134.68, 131.04, 129.75, 129.14, 128.76, 120.20, 120.10, 118.95, 118.73.

(*E*)-1, 3-bis (2-hydroxyphenyl) prop-2-en-1-one MC6



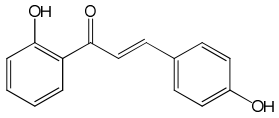
Yellow Crystals (recrystalized from Ethanol); Mp = 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.90 (s, OH), 8.18(d, *J*= 15.29HZ, 1H), 7.93 (dd, *J*= 1.56HZ, *J*= 8.23HZ, 1H), 7.85 (d, *J*= 15.29HZ, 1H), 7.61 (dd, *J*= 1.56HZ, *J*= 7.84HZ, 1H), 7.50 (t, *J*= 7.84HZ, 1H), 7.29 (t, *J*= 8.23HZ, 1H), 7.02 (t, *J*= 8.23HZ, 1H), 6.94 (t, *J*= 7.44HZ, 1H), 6.84 (d, *J*= 8.23HZ, 1H), 5.53 (bs, OH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.45, 163.60, 155.45, 141.00, 136.37, 132.10, 130.35, 129.90, 121.37, 118.92, 118.65, 116.58.

(*E*)-1-(2-hydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one MC7



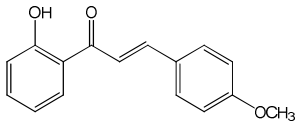
Orange Crystals (recrystalized from Ethanol); Mp = 148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.79 (s, OH), 7.93(d, *J*=7.36 HZ, 1H), 7.86 (d, *J*= 15.94HZ, 1H), 7.63 (d, *J*= 15.94HZ, 1H), 7.51 (t, *J*= 7.76HZ, 1H), 7.31 (t, *J*= 8.58HZ, 2H), 7.14 (s, 1H), 7.05 (d, *J*= 8.17HZ, 1H), 6.91-6.97 (m, 2H), 5.10 (bs, OH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.74, 163.64, 155.98, 144.99, 136.50, 130.29, 129.66, 121.62,120.59, 118.67, 118.02, 114.84.

(*E*)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one MC8



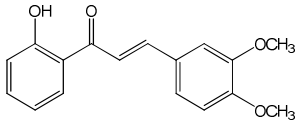
Yellow solid; Mp = 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.96 (s, OH), 7.82(d, *J*=15.57 HZ, 1H), 7.82 (d, *J*= 8.38HZ, 2H), 7.58 (t, *J*= 8.68HZ, 1H), 7.49 (t, *J*= 9.27HZ, 1H), 7.03 (d, *J*= 8.08HZ, 1H), 6.97 (d, *J*= 8.98HZ, 3H), 6.91 (d, *J*=8.86HZ, 1H), 6.04 (bs, OH); ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.32, 161.65, 158.45, 145.53, 136.34, 132.61, 130.91, 129.93,129.67, 120.17, 118.93, 117.53, 116.14.

(*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one MC9



Yellow solid; Mp = 91°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.94 (s, OH), 7.88-7.94(m, 2H), 7.63 (d, *J*= 8.04HZ, 2H), 7.54 (d, *J*= 16.11HZ, 1H), 7.48 (t, *J*= 8.05HZ, 1H), 7.02 (d, *J*= 8.05HZ, 1H), 6.95 (d, *J*= 8.63HZ, 3H), 3.86 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.76, 163.64, 162.11, 145.45, 136.25, 130.66, 129.64, 127.40, 120.20, 118.86, 118.67, 117.63, 114.61, 55.54.

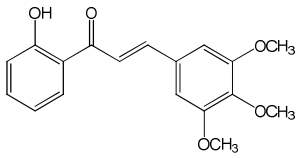
(*E*)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one MC10



Yellowsolid; Mp = 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.99 (s, OH), 7.91(d, *J*= 8.71 HZ, 1H), 7.84 (d, *J*= 15.75HZ, 1H), 7.42-7.52 (m, 2H), 7.22 (d, *J*= 7.71HZ, 1H), 7.15 (s, 1H), 7.00 (d, *J*= 8.38HZ, 1H), 6.85-6.93 (m, 2H), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.65, 163.64, 151.89, 149.38, 145.75,

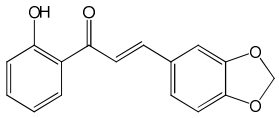
136.27, 129.63, 127.66, 123.71, 120.17, 118.83, 118.68, 117.83, 111.23, 110.33, 56.12, 56.09.

(*E*)-1-(2-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one MC11



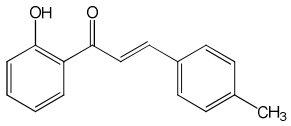
Yellow solid; Mp = 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.86 (s, OH), 7.92 (dd, *J*= 1.52HZ, *J*= 8.21HZ, 1H), 7.84 (d, *J*= 15.21HZ, 1H), 7.53 (d, *J*= 15.21HZ, 1H), 7.48 (d, *J*= 8.21HZ, 1H), 7.03 (d, *J*= 8.82HZ, 1H), 6.94 (t, *J*= 8.21HZ, 1H), 6.88 (s, 2H), 3.93 (s, 6H, $2OCH_3$), 3.91 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.59, 163.67, 153.61, 145.72, 140.91, 136.45, 130.13, 129.69, 120.09, 119.33, 118.89, 118.72, 108.02, 61.12, 56.35.

(*E*)-3-(benzo[d][1,3]dioxol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one MC12



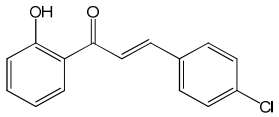
Yellow solid; Mp = 135°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.81 (s, OH), 7.83 (d, *J*= 8.45HZ, 1H), 7.78 (d, *J*= 15.37HZ, 1H), 7.39-7.43 (m, 2H), 7.10 (s, 1H), 7.07 (d, *J*= 8.45HZ, 1H), 6.94 (d, *J*= 8.84HZ, 1H), 6.86 (t, *J*= 7.68HZ, 1H), 6.78 (d, *J*= 8.07HZ, 1H), 5.96 (s, 2H, O-CH_2-O); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.62, 163.65, 150.[39,] 148.60, 145.41, 136.30, 129.60, 129.17, 125.82, 120.15, 118.87, 118.83, 108.84, 106.83, 101.84.

(*E*)-1-(2-hydroxyphenyl)-3-p-tolylprop-2-en-1-one MC13



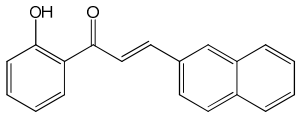
Yellow solid; Mp = 115°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.89 (s, OH), 7.88-7.94(m, 2H), 7.59 (d, *J*= 15.82HZ, 1H), 7.54 (d, *J*= 8.20HZ, 2H), 7.47 (t, *J*= 7.03HZ, 1H), 7.22 (d, *J*= 7.62HZ, 2H), 7.01 (d, *J*= 8.20HZ, 1H), 6.92 (t, J=7.62 HZ, 1H), 2.37 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.87, 163.67, 145.68, 141.71, 136.37, 131.96, 129.71, 128.82, 120.16, 118.90, 118.70,21.69.

(*E*)-3-(4-chlorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one MC14



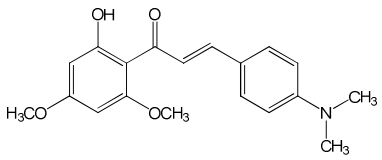
Golden yellow solid; Mp = 149°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.75 (s, OH), 7.89(d, *J*=7.69, 1H), 7.84 (d, *J*= 15.11HZ, 1H), 7.55-7.63 (m, 3H), 7.49 (t, *J*= 7.41HZ, 1H), 7.39 (d, *J*= 8.26HZ, 2H), 7.02 (d, *J*= 8.26HZ, 1H), 6.94 (t, J=7.69 HZ, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.54, 163.71, 144.01, 136.96, 136.65, 131.16, 129.88, 129.44, 120.65, 120.01, 118.99, 118.78.

(*E*)-1-(2-hydroxyphenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC15



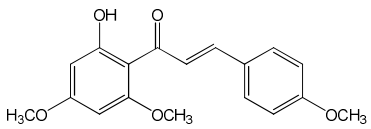
Yellow crystals (recrystalized from Ethanol); Mp = 135°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.86 (s, OH), 8.09(d, *J*=15.83, 2H), 7.99 (d, *J*= 7.70HZ, 1H), 7.76-7.92 (m, 6H), 7.50-7.56 (m, 2H), 7.05 (d, *J*= 8.55HZ, 1H), 6.97 (t, *J*=7.70 HZ, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.76, 163.72, 145.65, 136.51, 134.64, 133.42, 132.18, 131.25, 129.77, 128.94, 128.84, 127.93, 127.73, 126.98, 123.74, 120.26, 120.17, 118.96, 118.75.

(*E*)-3-(4-(dimethylamino) phenyl)-1-(2-hydroxy-4, 6-dimethoxyphenyl) prop-2-en-1-one MC16



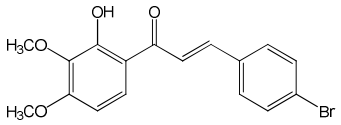
Dark orange solid; Mp = 138°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.03 (s, OH), 7.78(d, *J*=14.02, 1H), 7.70 (d, *J*= 9.18HZ, 2H), 7.50 (d, *J*=14.41, 1H), 6.67 (d, *J*= 9.18HZ, 2H), 6.04 (d, *J*= 2.44HZ, 1H), 5.91 (d, *J*=2.44 HZ, 1H), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.06 (s, 6H, 2xCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.64, 168.27, 166.18, 162.30, 161.17, 142.77, 129.86, 127.92, 125.18, 114.37, 106.30, 93.38, 91.45, 55.78, 40.61, 40.28.

(*E*)-1-(2-hydroxy-4, 6-dimethoxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one MC17



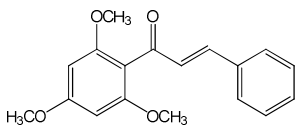
Yellow solid; Mp = 110°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.41 (s, OH), 7.79(s, 2H), 7.57 (d, *J*= 8.77HZ, 2H), 6.93 (d, *J*=8.29, 1H), 6.10 (d, *J*= 2.92HZ, 1H), 5.90 (d, *J*= 2.92HZ, 1H), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.68, 168.45, 166.09, 162.53, 161.42, 142.57, 130.20, 128.37, 125.18, 114.43, 106.41, 93.86, 91.32, 55.93, 55.67, 55.48.

(*E*)-3-(4-bromophenyl)-1-(2-hydroxy-3, 4-dimethoxyphenyl) prop-2-en-1-one MC18



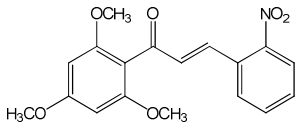
Yellow solid; Mp = 152°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.12 (s, OH), 7.82 (d, *J*= 15.49HZ, 1H), 7.67 (d, *J*=8.85, 1H), 7.49-7.59 (m, 5H), 6.54 (d, *J*= 8.85HZ, 1H), 3.96 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.23, 158.83, 158.43, 143.35, 136.85, 133.85, 132.36, 129.99, 126.15, 125.15, 120.86, 115.61, 103.03, 60.79, 56.27; IR (ATR): 2936, 1634, 1557, 1277, 1243, 1127, 1000, 790, 703 cm^{-1}; HRMS (ESI): calculated for $C_{17}H_{15}BrO_4H$ $[M+H]^+$ 362.0154 , found 362.0237.

(*E*)-3-phenyl-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one MC19



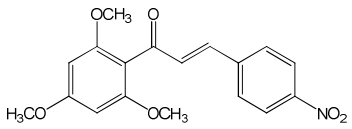
Golden- brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.52(m, 6H), 6.96 (d, *J*= 15.26HZ, 1H), 6.15 (s, 2H), 3.79 (s, 3H, OCH_3), 3.71 (s, 6H, 2x OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.48, 162.54, 158.43, 144.53, 135.02, 130.18, 129.53, 128.89, 128.08, 90.84, 55.92, 55.50.

(*E*)-3-(2-nitrophenyl)-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one MC20



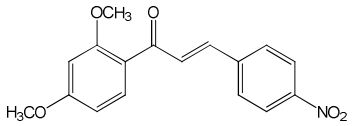
Yellow solid; Mp = 152°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00(d, *J*=8.07HZ, 1H), 7.62-7.72 (m, 3H), 7.51(t, *J*= 8.69HZ, 1H), 6.81(d, *J*= 15.53HZ, 1H), 6.15 (s, 2H), 3.84 (s, 3H, OCH_3), 3.77 (s, 6H, 2x OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.41, 162.84, 159.04, 139.87, 133.59, 131.39, 130.15, 129.35, 124.95, 110.53, 90.69, 55.93, 55.52

(*E*)-3-(4-nitrophenyl)-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one MC21



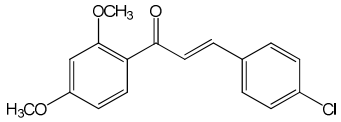
Yellow solid; Mp = 158°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24(d, *J*=8.35HZ, 2H), 7.67(d, *J*=8.84HZ, 2H), 7.44(d, *J*=15.72HZ, 1H), 7.08(d, *J*= 15.72HZ, 1H), 6.17 (s, 2H), 3.87 (s, 3H, OCH_3), 3.80 (s, 6H, 2x OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.86, 163.07, 159.33, 148.37, 141.37, 139.88, 132.50, 128.89, 124.14, 123.69, 111.45, 90.84, 56.05, 55.58.

(*E*)-1-(2, 4-dimethoxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one MC22



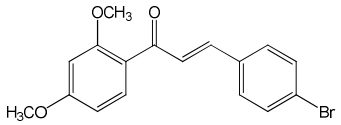
Yellow solid; Mp = 172°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25(d, *J*=8.49Hz, 2H), 7.82(d, *J*=8.49Hz, 1H), 7.73(d, *J*=7.92Hz, 2H), 7.67(s, 2H), 6.59 (dd, *J*=2.26Hz, *J*=8.82Hz, 1H), 6.51(d, *J*=2.83Hz, 1H), 3.94 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 189.29, 164.84, 160.76, 148.33, 141.93, 138.34, 133.45, 130.98, 128.71, 123.43, 105.56, 98.44, 55.83, 55.64.

(*E*)-3-(4-chlorophenyl)-1-(2, 4-dimethoxyphenyl)prop-2-en-1-one MC23



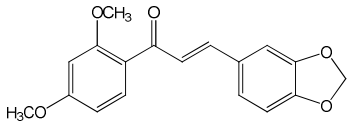
Pale yellow solid; Mp = 125°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.77(m, 1H), 7.62(d, *J*=15.79Hz, 1H), 7.49-7.53(m, 2H), 7.35(d, *J*=8.88Hz, 1H), 7.10(d, *J*=8.24Hz, 1H), 6.92(d, *J*=8.92Hz, 1H), 6.56(d, *J*=8.58Hz, 1H), 6.46-6.49(m, 1H), 3.90 (s, 3H, OCH_3), 3.86(s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.07, 164.38, 160.50, 140.36, 139.34, 132.68, 129.88, 129.44, 129.29, 127.63, 121.96, 105.31, 98.44, 55.58, 55.51.

(*E*)-3-(4-bromophenyl)-1-(2, 4-dimethoxyphenyl) prop-2-en-1-one MC24



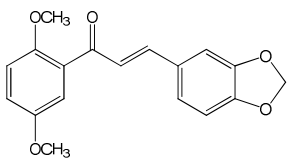
Yellow solid; Mp = 122°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.77(m, 1H), 7.60(d, *J*=16.02HZ, 1H), 7.48-7.54(m, 2H), 7.44(d, *J*=8.20Hz, 1H), 7.26(d, *J*=2.34Hz, 1H), 6.86(d, *J*=8.20Hz, 1H), 6.56(dd, *J*=2.34Hz, *J*=9.37, 1H), 6.49(d, *J*=2.34, 1H), 3.90 (s, 3H, OCH_3), 3.86(s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.06, 164.79, 164.33, 140.39, 137.72, 135.78, 133.37, 133.13, 129.65, 127.69, 121.94, 105.26, 98.43, 55.76, 55.64.

(*E*)-3-(benzo[d] [1, 3] dioxol-5-yl)-1-(2, 4-dimethoxyphenyl) prop-2-en-1-one MC25



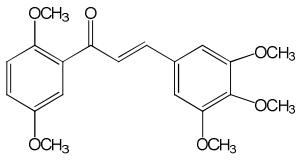
Yellow solid; Mp = 119°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74(dd, *J*=2.59Hz, *J*=8.63Hz, 1H), 7.60(d, *J*=16.83Hz, 1H), 7.34(d, *J*=15.97Hz, 1H), 7.11(s, 1H), 7.04-7.06(m, 1H), 6.80(dd, J=3.88Hz, *J*=8.63Hz, 1H), 6.55(d, *J*=8.63Hz, 1H), 6.48(s, 1H), 5.99 (s, 2H), 3.89 (s, 3H, OCH_3), 3.85(s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.44, 164.23, 160.36, 149.54, 147.77, 141.80, 132.76, 129.86, 125.18, 124.86, 122.27, 108.71, 106.45, 104.68, 101.61, 98.55, 55.83, 55.62.

(*E*)-3-(benzo[d] [1, 3] dioxol-5-yl)-1-(2, 5-dimethoxyphenyl) prop-2-en-1-one MC26



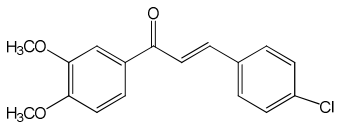
Yellow solid; Mp = 112°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55(d, *J*=15.06Hz, 1H), 7.24(d, *J*=15.54Hz, 1H), 7.17(d, *J*=2.91Hz, 1H), 7.10(s, 1H), 7.05(d, *J*=8.26Hz, 1H), 7.00(dd, J=3.41Hz, *J*=9.23Hz, 1H), 6.92(d, *J*=9.23Hz, 1H), 6.80(d, *J*=8.26Hz, 1H), 5.98 (s, 2H), 3.83 (s, 3H, OCH_3), 3.78(s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.36, 153.68, 152.55, 149.77, 148.40, 143.30, 129.92, 125.14, 119.02, 114.50, 113.46, 108.67, 106.74, 101.64, 56.59, 56.11.

(*E*)-1-(2, 5-dimethoxyphenyl)-3-(3, 4, 5-trimethoxyphenyl) prop-2-en-1-one MC27



Yellow solid; Mp = 123°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51(d, *J*=15.83Hz, 1H), 7.27(d, *J*=15.83Hz, 1H), 7.15(d, *J*=3.34Hz, 1H), 7.03(dd, J=3.12Hz, *J*=8.92Hz, 1H),6.94(d, *J*=8.47Hz, 1H), 6.81(s, 2H), 3.88(d, *J*=s, 9H, 3xOCH_3), 3.83 (s, 3H, OCH_3), 3.81(s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.68, 153.69, 153.49, 152.46, 143.80, 140.26, 130.68, 129.84, 126.43, 118.93, 114.46, 113.50, 105.64, 61.09, 56.62, 55.96.

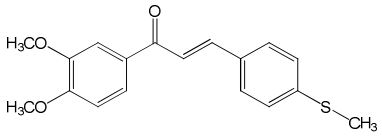
(*E*)-3-(4-chlorophenyl)-1-(3, 4-dimethoxyphenyl) prop-2-en-1-one MC28



Yellow solid; Mp = 101°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68(d, *J*=15.82Hz, 1H), 7.53-7.55(m, 3H), 7.36-7.41 (m, 3H), 7.20 (s, 1H), 7.03(d, *J*=16.22Hz, 1H), 3.97(s, 6H,

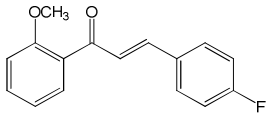
2x OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.33, 157.58, 142.07, 136.51, 133.18, 130.99, 129.51, 129.17, 125.52, 110.17, 108.95, 52.42, 51.90.

(*E*)-1-(3, 4-dimethoxyphenyl)-3-(4-(methylthio) phenyl) prop-2-en-1-one MC29



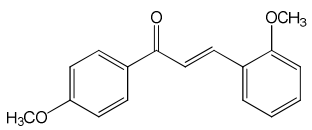
Yellow solid; Mp = 92°C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77(d, *J*=15.26Hz, 1H), 7.68(d, *J*=7.63Hz, 1H), 7.62 (s, 1H), 7.55 (t, *J*=8.39Hz, 2H), 7.23(d, *J*=7.63Hz, 3H), 6.93(d, *J*=8.39Hz, 1H), 3.96 (s, 6H, 2x OCH_3), 2.52(s, 3H, S-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.57, 153.28, 149.30, 143.54, 142.17, 131.63, 131.48, 128.83, 126.03, 123.03, 120.64, 110.82, 110.03, 56.18, 56.14, 15.23.

(*E*)-3-(4-fluorophenyl)-1-(2-methoxyphenyl) prop-2-en-1-one MC30



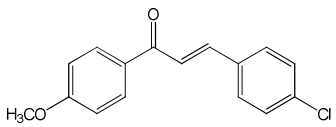
Pale yellow solid; Mp = 107°C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57-7.60 (m, 1H), 7.51-7.54 (m, 2H), 7.32-7.47 (m, 4H), 7.23 (d, *J*=15.80Hz, 1H), 6.95-7.04 (m, 2H), 3.88 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.29, 160.70, 158.02, 143.43, 132.66, 130.18, 128.73, 128.40, 127.43, 125.66, 120.66, 115.30, 111.66, 55.85.

(*E*)-3-(2-methoxyphenyl)-1-(4-methoxyphenyl) prop-2-en-1-one MC31



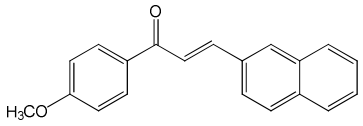
Yellow solid; Mp = 51°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03(d, *J*=8.58Hz, 2H), 7.76(d, *J*=15.37Hz, 1H), 7.52(d, *J*=15.72Hz, 1H), 7.33(t, *J*=7.86Hz, 1H), 7.24-7.25 (m, 1H), 7.15-7.17 (m, 1H), 6.94-6.98 (m, 3H), 3.89 (s, 3H, OCH_3), 3.86(s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.82, 163.53, 160.01, 143.98, 136.55, 131.14, 130.93, 130.00, 122.28, 121.09, 116.14, 113.94, 113.47, 55.60, 55.45.

(*E*)-3-(4-chlorophenyl)-1-(4-methoxyphenyl) prop-2-en-1-one MC32



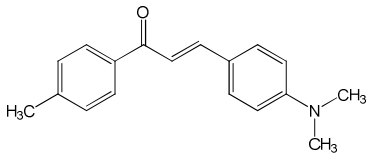
Yellow solid; Mp = 135°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03(d, *J*=8.16Hz, 2H), 7.75(d, *J*=16.33Hz, 1H), 7.57(d, *J*=8.16Hz, 2H), 7.51(d, *J*=16.33Hz, 1H),7.38(d, *J*=9.07Hz, 2H), 6.99 (d, *J*=9.28Hz, 2H), 3.90 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.49, 163.63, 142.55, 136.27, 133.66, 130.93, 129.59, 129.29, 122.36, 113.98, 55.61.

(*E*)-1-(4-methoxyphenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC33



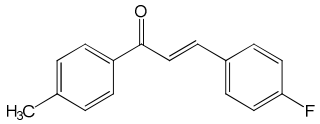
Golden yellow solid; Mp = 155°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08(d, *J*=8.09Hz, 2H), 8.02 (s, 1H), 7.96(d, *J*=15.32Hz, 1H), 7.79-7.89 (m, 4H), 7.66(d, *J*=15.36Hz, 1H), 7.48-7.54 (m, 2H), 6.99 (d, *J*=8.94Hz, 2H), 3.88 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.76, 163.53, 144.14, 130.94, 130.54, 128.76, 128.71, 127.88, 127.36, 126.82, 123.80, 122.07, 113.95, 55.60.

(*E*)-3-(4-(dimethylamino) phenyl)-1-p-tolylprop-2-en-1-one MC34



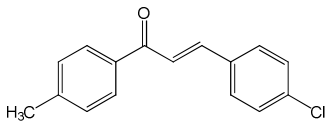
Yellow solid; Mp = 132°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92(d, *J*=8.21Hz, 2H), 7.78(d, *J*=15.45Hz, 1H), 7.54(d, *J*=8.69Hz, 2H), 7.34(d, *J*=15.40Hz, 1H),7.27(d, *J*=7.24Hz, 2H), 6.68 (d, *J*=8.69Hz, 2H), 3.39 (s, 6H, 2xCH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.28, 152.04, 145.49, 142.95, 136.51, 130.43, 129.25, 128.54, 122.82, 116.99, 111.90, 40.23, 21.73.

(*E*)-3-(4-fluorophenyl)-1-p-tolylprop-2-en-1-one MC35



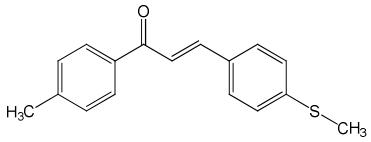
Golden yellow solid; Mp = 145°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93(d, *J*=8.16Hz, 2H), 7.76(d, *J*=15.86Hz, 1H), 7.62(dd, *J*=8.69Hz, *J*=5.89, 2H), 7.46(d, *J*=15.86Hz, 1H),7.30(d, *J*=8.62Hz, 2H), 7.10 (t, *J*=8.16Hz, 2H), 2.42 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 189.86, 165.33, 162.81, 143.83, 143.15, 135.61, 131.31, 130.34, 129.44, 128.65, 121.85, 116.29, 21.78.

(*E*)-3-(4-chlorophenyl)-1-p-tolylprop-2-en-1-one MC36



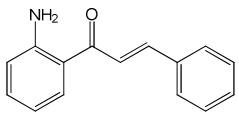
Yellow solid; Mp = 144°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92(d, *J*=8.10Hz, 2H), 7.75(d, *J*=15.82Hz, 1H), 7.62(dd, *J*=8.65Hz, *J*=6.02, 2H), 7.45(d, *J*=15.86Hz, 1H),7.29(d, *J*=8.65Hz, 2H), 7.10 (t, *J*=8.36Hz, 2H), 2.42 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 189.73, 165.28, 162.74, 143.77, 143. 06, 135.64, 131.34, 130.39, 129.40, 128.57, 121.86, 116.20, 21.78.

(E)-3-(4-(methylthio) phenyl)-1-p-tolylprop-2-en-1-one MC37



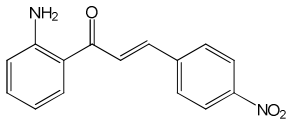
Pale yellow solid; Mp = 142°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96(d, *J*=8.75Hz, 2H), 7.77(d, *J*=16.41Hz, 1H), 7.65(d, *J*=8.05Hz, 2H), 7.21-7.29(m, 3H),6.73(d, *J*=8.75Hz, 2H), 2.52 (s, 3H, CH_3), 2.32 (s, 3H, S- CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 189.20, 144.89, 142.82, 133.13, 131.23, 129.58, 128.13, 126.98, 126.33, 126.00, 120.43, 21.25, 15.61.

(*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one MC38



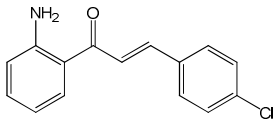
Golden yellow solid; Mp = 66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J*=8.51Hz, 1H), 7.73 (d, *J*=15.14Hz, 1H), 7.58-7.64(m, 3H), 7.36-7.42 (m, 3H), 7.24-7.29 (m, 1H), 6.97-6.71(m, 2H), 6.33 (bs, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.84, 151.21, 143.08, 135.35, 134.57, 131.34, 130.18, 129.02, 128.51, 123.35, 119.09, 117.55, 115.87.

(*E*)-1-(2-aminophenyl)-3-(4-nitrophenyl) prop-2-en-1-one MC39



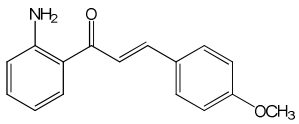
Orange solid; Mp = 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J*=8.41Hz, 3H), 7.67-7.90 (m, 6H), 7.32(t, *J*=7.65Hz, 1H), 6.69 (bs, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 190.70, 169.90, 151.49, 148.26, 141.45, 139.71, 135.18, 131.15, 128.76, 127.05, 124.53, 117.59, 115.98.

(*E*)-1-(2-aminophenyl)-3-(4-chlorophenyl) prop-2-en-1-one MC40



Pale yellow solid; Mp = 143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J*=8.09Hz, 1H), 7.67 (d, *J*=15.21Hz, 1H), 7.54 (d, *J*=8.79Hz, 2H), 7.37 (d, *J*=8.79Hz, 2H), 7.24-7.33 (m, 2H), 6.63-6.67 (m, 2H), 6.37 (bs, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.40, 171.27, 151.25, 141.55, 136.06, 134.53, 133.90, 131.09, 129.56, 129.04, 123.69, 117.44, 115.91.

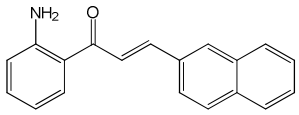
(*E*)-1-(2-aminophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one MC41



Yellow solid; Mp = 152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J*=8.46Hz, 1H), 7.66 (d, *J*=15.23Hz, 1H), 7.52 (d, *J*=8.80Hz, 2H), 7.44 (d, *J*=15.23Hz, 1H), 7.21-7.24

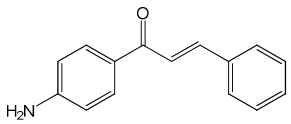
(m, 1H), 6.87 (d, *J*=8.12Hz, 2H), 6.60-6.65 (m, 2H), 6.22 (bs, 2H, NH_2), 3.78 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.83, 161.40, 151.08, 142.90, 134.21, 131.04, 130.11, 128.06, 120.82, 119.35, 117.43, 115.89, 114.41, 55.47.

(*E*)-1-(2-aminophenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC42



Golden yellow crystals (recrystalized from ethanole); Mp = 148°C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.21(s, 1H), 7.78-7.94 (m, 5H), 7.79 (d, *J*=8.91Hz, 1H), 7.73(d, *J*=15.37Hz, 1H), 7.49-7.54 (m, 2H), 7.30 (t, *J*=8.80Hz, 1H), 6.70-6.74 (m, 2H), 6.35 (bs, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.73, 151.15, 143.12, 134.44, 134.39, 133.51, 132.45, 131.16, 130.25, 128.73, 128.69, 127.24, 126.92, 126.78, 123.89, 123.35, 119.92, 117.44, 115.99; IR (ATR): 3378, 1609, 1568, 1540, 1359, 1247, 1153, 1008, 810, 737cm^{-1}; HRMS (ESI): calculated for $C_{19}H_{15}NOH$ $[M+H]^+$ 274.1232 , found 274.1486 and $C_{19}H_{15}NOH_2$ $[M+2H]^+$ 275.1310, found 275.1120.

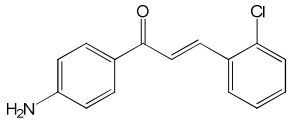
(*E*)-1-(4-aminophenyl)-3-phenylprop-2-en-1-one MC43



Dark yellow solid; Mp = 172 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J*=8.61Hz, 2H), 7.82 (d, *J*=14.64Hz, 1H), 7.55-7.64(m, 2H), 7.34-7.41 (m, 3H), 6.68 (d, *J*=8.30Hz, 2H), 6.57 (t, *J*=8.63Hz, 1H), 4.07 (s, 2H, NH_2); ^{13}C NMR (400 MHz,

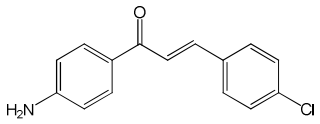
$CDCl_3$): δ 188.28, 151.36, 143.12, 135.38, 133.66, 131.26, 130.18, 128.95, 126.23, 122.16, 114.03.

(*E*)-1-(4-aminophenyl)-3-(2-chlorophenyl) prop-2-en-1-one MC44



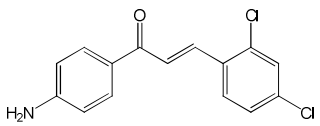
Dark yellow solid; Mp = 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J*=15.63Hz, 1H), 7.92 (d, *J*=8.52Hz, 2H), 7.47 (d, *J*=15.63Hz, 1H), 7.41-7.46(m, 2H), 7.28-7.34 (m, 2H), 6.69 (d, *J*=7.81Hz, 2H), 4.09 (s, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.06, 151.46, 139.02, 135.35, 133.75, 131.46, 130.82, 130.42, 128.22, 127.79, 127.05, 124.96, 114.02.

(*E*)-1-(4-aminophenyl)-3-(4-chlorophenyl) prop-2-en-1-one MC45



Dark yellow solid; Mp = 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J*=8.25Hz, 2H), 7.72 (d, *J*= 15.22Hz, 1H), 7.49-7.57(m, 3H), 7.36 (d, *J*=8.32Hz, 2H), 6.69 (d, *J*=8.32Hz, 2H), 4.09 (s, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 187.88, 151.40, 141.75, 135.97, 133.88, 131.21, 129.37, 129.11, 128.32, 122.52, 114.03.

(*E*)-1-(4-aminophenyl)-3-(2, 4-dichlorophenyl)prop-2-en-1-one MC46



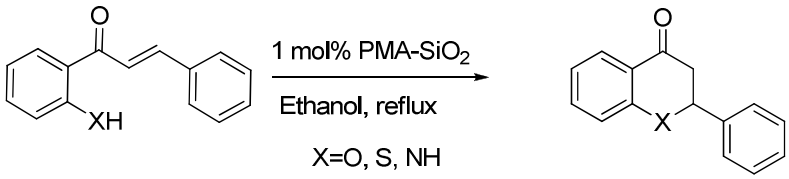
Orange crystals (recrystalized from Ethanole); Mp = 184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J*=14.81Hz, 1H), 7.91 (d, *J*= 8.31Hz, 2H), 7.66 (d, *J*= 7.73Hz, 1H),7.48 (d, *J*=14.81Hz, 2H), 7.27-7.30 (m, 2H), 6.70(d, *J*=7.08Hz, 2H), 4.17 (s, 2H, NH_2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 187.92, 151.49, 137.79, 135.85, 132.51, 131.32, 130.13, 128.52, 127.52, 125.24, 114.03.

Procedure for preparation of PMA / SiO_2 (1 mol %):

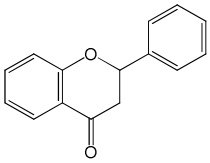
PMA/SiO_2 was prepared by adding 0.1 equivalent of phosphoMolibdic acid ($H_3PMo_{12}O_{40}$) and 0.9 equivalents silica gel (100-200 mesh) in Methanol and stirring at room temperature for around six hours. Methanol was removed under reduced pressure and PMA/SiO_2 was yielded as a yellow solid (Kumar *et al*. 2004).

General procedure for preparation of Flavanones MF1- MCF17:

A mixture of PMA-SiO_2 (1 mol %), 2′-hydroxychalcones, 2′-aminochalcones and 2′-mercaptochalcones in ethanol (5 ml / mmol of chalcone) under N_2 atmosphere was stirred under reflux for the appropriate time (8-18 hrs). The reaction monitored by TLC, after completion of the reaction, the solvent was removed under reduced pressure and the residue was dissolved in diethylether (10 ml) and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel 100-200 mesh) using *n*-hexane/ ethyl acetate as eluent to afford pure flavanone **MF1-MF17**. The filtered catalyst was reused after drying.

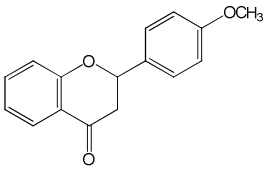


2-phenylchroman-4-one MF1



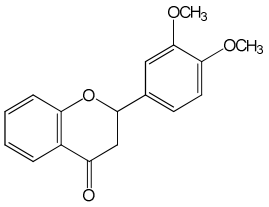
Light yellow solid; Mp = 95 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.86 (m, 1H), 7.29-7.46 (m, 6H), 6.96-7.01(m, 2H), 5.41 (dd, *J*=2.86Hz, *J*=13.37Hz , 1H), 3.01 (dd, *J*=13.44Hz, *J*=16.78Hz, 1H), 2.82 (dd, *J*=2.86Hz, *J*=16.88Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 191.99, 161.57, 138.75, 136.22, 129.05, 128.87, 128.79, 128.68, 127.06, 126.16, 121.63, 120.94, 118.15, 79.62, 44.69.

2- (4-methoxyphenyl) chroman-4-one MF2



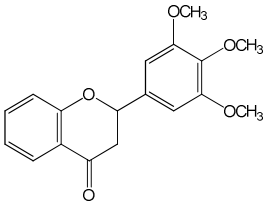
Yellow solid; Mp = 153 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.84 (d, *J*= 7.86 Hz, 1H), 7.39-7.43 (m, 1H), 7.32(d, *J*= 8.94 Hz, 2H), 6.97 (t, *J*=7.84 Hz, 2H), 6.87 (d, *J*=8.94Hz, 2H), 5.34 (dd, *J*=3.30Hz, *J*=13.65Hz , 1H), 3.74 (s, 3H), 3.02 (dd, *J*=13.90Hz, *J*=16.62Hz, 1H), 2.78 (dd, *J*=3.39Hz, *J*=16.96Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 192.35, 161.73,160.05, 136.26, 130.84, 127.84, 127.12,121.62, 121.00, 118.23, 114.61, 114.29, 77.47, 55.45, 44.54.

2- (3, 4- dimethoxyphenyl) chroman-4-one MF3



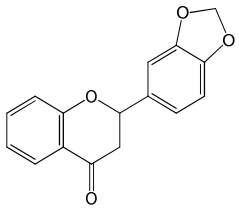
Yellow solid; Mp = 152 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.93 (dd, *J*= 7.93Hz, *J*= 1.93 Hz, 1H), 7.48-7.53 (m, 1H), 7.02-7.07 (m, 4H), 6.91 (d, *J*=7.97 Hz, 1H), 5.43 (dd, *J*=2.5Hz, *J*=13.38Hz , 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.13 (dd, *J*=13.39Hz, *J*=16.72Hz, 1H), 2.87 (dd, *J*=3.30Hz, *J*=16.73Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 192.24, 161.63, 149.52, 149.34, 136.28, 127.14, 121.68, 121.00, 118.92, 118.23, 111.21, 109.48, 79.66, 56.07, 44.68; IR (ATR): 3004, 2944, 1689, 1603, 1462, 1259, 1141, 1065, 1023, 758 cm $^{-1}$. HRMS (ESI): calculated for $C_{17}H_{16}O_4H$ $[M+H]^+$ 285.1049, found 285.1352.

2- (3, 4, 5- trimethoxyphenyl) chroman-4-one MF4



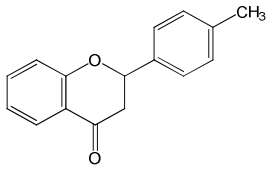
Yellow solid; Mp = 136 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.94 (dd, *J*= 8.22Hz, *J*= 1.91Hz, 1H), 7.50-7.54 (m, 1H), 7.05-7.09 (m, 2H), 6.91 (s, 2H), 5.42 (dd, *J*=3.37 Hz, *J*=13.49Hz , 1H), 3.89 (s, 6H), 3.87 (s, 3H), 3.10 (dd, *J*=13.49Hz, *J*=16.86Hz, 1H), 2.88 (dd, *J*=3.38Hz, *J*=16.71Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ =192.04, 161.51, 153.64, 138.28, 136.36, 134.38, 127.16, 121.84, 120.98, 118.23, 103.30, 79.96,60.96, 56.29, 44.95.

2- (benzo [*d*][1, 3] dioxol-5-yl) chroman-4-one MF5



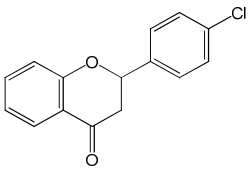
Yellow solid; Mp = 127 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.93 (d, *J*= 8.54Hz,1H), 7.49-7.53 (m, 1H), 7.00-7.09 (m, 3H), 6.91 (d, *J*= 8.03Hz,1H), 6.84 (d, *J*= 7.58Hz,1H), 6.00 (s,2H), 5.39 (dd, *J*=3.40 Hz, *J*=13.60Hz , 1H), 3.06 (dd, *J*=13.60Hz, *J*=16.15Hz, 1H), 2.85(dd, *J*=3.42Hz, *J*=16.45Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ =192.15, 161.57, 148.17,148.09, 136.32, 132.60, 127.14, 121.72, 120.95, 120.16, 118.21, 108.51, 106.89, 79.59, 44.74.

2- *p*- tolylchroman-4-one MF6



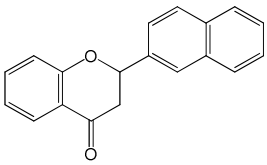
Light yellow solid; Mp = 86 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.86 (dd, *J*= 1.68 Hz, *J*= 8.08 Hz 1H), 7.41-7.45 (m, 1H), 7.29(d, *J*= 8.08 Hz, 2H), 7.18(d, *J*= 8.75 Hz, 2H), 6.96-6.99 (m, 2H), 5.39 (dd, *J*=2.49Hz, *J*=13.45Hz , 1H), 3.03 (dd, *J*=13.82Hz, *J*=17.01Hz, 1H), 2.80 (dd, *J*=2.71Hz, *J*=17.05Hz, 1H), 2.31(s, 3H);^{13}C NMR (100MHz, $CDCl_3$): δ 192.33, 161.72,138.83, 136.28, 135.81, 129.60, 127.13,126.29, 121.64,121.00, 118.25,77.47, 44.65, 21.31.

2- (4- clorophenyl) chroman-4-one MF7



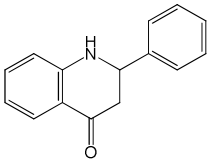
Yellow solid; Mp = 185 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.85 (dd, *J*= 2.17 Hz, *J*= 7.98 Hz 1H), 7.42-7.46 (m, 1H), 7.30-7.38(m, 4H), 6.95-7.01(m, 2H), 5.39 (dd, *J*=3.40Hz, *J*=13.62Hz , 1H), 2.97 (dd, *J*=13.65Hz, *J*=17.03Hz, 1H), 2.80 (dd, *J*=3.45Hz, *J*=17.25Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 191.49, 161.30,137.27, 136.29, 134.57, 129.34, 128.79, 127.08, 121.80, 120.89, 118.08,78.81, 44.58.

2- (naphtalen-2-yl) chroman-4-one MF8



Orange solid; Mp = 188 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.84-7.96 (m, 5H), 7.45-7.59 (m, 4H), 7.04-7.09(m, 2H), 5.62 (dd, *J*=2.93Hz, *J*=13.36Hz , 1H), 3.17 (dd, *J*=13.52Hz, *J*=16.98Hz, 1H), 2.96 (dd, *J*=2.71Hz, *J*=16.98Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 192.02, 161.64, 136.35, 133.47, 133.26, 128.84, 128.28, 127.91, 127.84, 127.19, 126.98, 126.65, 125.50, 123.74, 121.75, 121.08, 118.27, 79.80, 44.75.

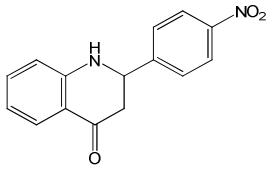
2- phenyl-2, 3-dihydroquinolin-4-(1H)-one MF9



Yellow solid; Mp = 145°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.89 (d, *J*= 8.15Hz, 1H), 7.32-7.50 (m, 6H), 6.80 (t, *J*=7.95 Hz, 1H), 6.72 (d, *J*=8.16 Hz, 1H), 4.76 (dd,

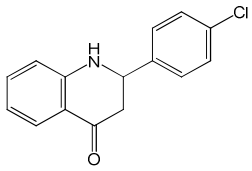
J=3.21Hz, *J*=13.67Hz , 1H), 4.50 (bs, NH), 2.90 (dd, *J*=13.67Hz, *J*=17.70Hz, 1H), 2.80 (dd, *J*=3.21Hz, *J*=17.23Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 193.41, 151.64, 141.09, 135.51, 129.09, 128.57, 127.71, 126.72, 119.11, 118.55, 116.00, 58.61, 46.55; IR (ATR): 3328, 1651, 1602, 1331, 1153, 761, 698 cm^{-1}; HRMS (ESI): calculated for $C_{15}H_{13}NOH$ $[M+H]^+$ 224.0997, found 224.1079.

2- (4-nitrophenyl)-2, 3-dihydroquinolin-4-(1H)-one MF10



Dark orange solid; Mp = 193 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.20 (d, *J*= 8.93Hz, 2H), 7.81 (dd, *J*= 8.03Hz, *J*= 1.70 Hz, 1H), 7.59 (d, *J*= 8.95 Hz, 2H), 7.47(d, *J*= 8.93 Hz, 1H), 6.78 (dt, *J*=7.82 Hz, *J*= 1.68 Hz, 1H),6.70(d, *J*= 8.19 Hz, 1H), 4.83 (dd, *J*=6.71Hz, *J*=10.06Hz , 1H), 4.46 (bs, NH), 2.76- 2.79 (m, 2H);^{13}C NMR (100MHz, $CDCl_3$): δ 192.52, 151.09, 148.49, 135.71,127.69, 127.51, 126.99, 124.33, 123.75, 119.22, 116.04, 57.91, 46.11.

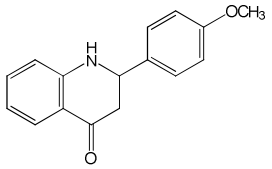
2- (4-clorophenyl)-2, 3-dihydroquinolin-4-(1H)-one MF11



Yellow solid; Mp = 171 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.87 (d, *J*= 8.12 Hz, 1H), 7.33-7.41 (m, 5H), 6.81 (t, *J*=7.71 Hz 1H), 6.72 (d, *J*=7.57 Hz, 1H), 4.74 (dd, *J*=3.45Hz, *J*=13.41Hz , 1H), 4.41 (bs, NH), 2.83 (dd, *J*=13.41Hz, *J*=16.60Hz, 1H), 2.74

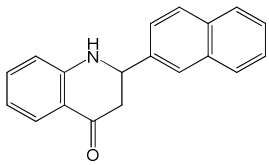
(dd, *J*=3.41Hz, *J*=15.95Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 193.00, 151.44, 139.61, 135.61, 134.25, 129.49, 128.09, 127.70, 119.14, 118.80, 116.06, 57.99, 46.51.

2- (4-methoxyphenyl)-2, 3-dihydroquinolin-4-(1H)-one MF12



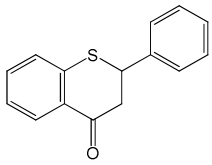
Yellow solid; Mp = 149 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.80 (d, *J*= 8.62 Hz, 1H), 7.23-7.32 (m, 3H), 6.85 (d, *J*= 8.56 Hz, 2H), 6.71 (t, *J*=8.01 Hz, 1H),6.61 (d, *J*= 8.05 Hz, 1H), 4.62 (dd, *J*=3.53Hz, *J*=13.21Hz , 1H), 4.39 (bs, NH), 3.74 (s, 3H), 2.79 (dd, *J*=13.58Hz, *J*=15.73Hz, 1H), 2.66 (dd, *J*=3.55Hz, *J*=16.05Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 193.81, 160.91, 151.15, 135.45, 132.55, 127.92, 127.71, 118.48, 115.96, 114.38, 58.02, 55.45, 46.63.

2- (naphthalen2-yl)-2, 3-dihydroquinolin-4-(1H)-one MF13



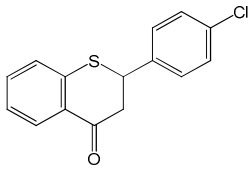
Yellow solid; Mp = 243 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.76- 7.83 (m, 5H), 7.50 (dd, *J*=1.77Hz, *J*=8.61Hz , 1H), 7.43-7.46 (m, 2H), 7.26 (td, *J*=1.51Hz, *J*=8.86Hz, 1H), 6.74 (t, *J*=7.59Hz, 1H), 6.68 (d, *J*=7.85Hz, 1H), 4.85 (dd, *J*=3.89Hz, *J*=13.62Hz , 1H), 4.51 (bs, NH), 2.91(dd, *J*=13.63Hz, *J*=16.87Hz, 1H), 2.77 (dd, *J*=3.85Hz, *J*=16.85Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 193.21, 151.55, 138.36, 135.46, 133.37, 133.32, 128.92, 127.94, 127.79, 127.68, 126.57, 126.38, 125.64, 124.29, 119.12, 118.56, 115.98, 58.66, 46.42; IR (ATR) 3315, 1654, 1606, 1478, 1115, 747, cm^{-1}; HRMS (ESI) calculated for $C_{19}H_{15}NOH$ $[M+H]^+$ 274.1154, found 274.1862.

2-phenylthiochroman-4-one MF14



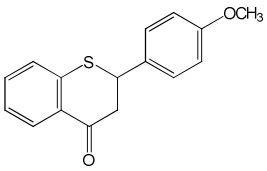
Golden yellow solid; Mp = 52 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.15 (d, *J*= 8.78 Hz, 1H), 7.28-7.49 (m, 7H), 7.21 (t, *J*=8.20 Hz, 1H), 4.73 (dd, *J*=3.65Hz, *J*=12.78Hz , 1H), 3.32 (dd, *J*=13.39Hz, *J*=15.92Hz, 1H), 3.20 (dd, *J*=3.04Hz, *J*=16.43Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 194.47, 142.18, 138.51, 133.77, 130.48, 129.30, 129.10, 128.57, 127.53, 127.32, 125.33, 46.75, 45.56; IR (ATR) 3059, 3030, 2949, 1673, 1585, 1435, 1284, 1084, 753, 695cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{12}OSH$ $[M+H]^+$ 241.0609, found 241.0687.

2-(4-clorophenyl) thiochroman-4-one MF15



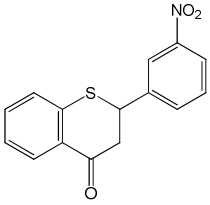
Light yellow solid; Mp = 122 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.14 (dd, *J*= 1.26Hz, *J*= 8.79 Hz, 1H), 7.26-7.46 (m, 7H), 4.69 (dd, *J*=2.99Hz, *J*=12.15Hz , 1H), 3.27 (dd, *J*=13.19Hz, *J*=16.74Hz, 1H), 3.19 (dd, *J*=3.15Hz, *J*=16.35Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 194.25, 145.95, 141.67, 135.63, 133.92, 132.13, 129.31, 127.31, 125.84, 125.40, 129.05, 46.96, 44.73.

2-(4-methoxyphenyl) thiochroman-4-one MF16



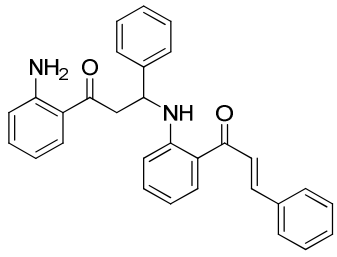
Yellow solid; Mp = 97 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.14 (d, *J*= 7.82Hz, 1H), 7.41(t, *J*= 6.98Hz, 1H), 7.32 (d, *J*= 8.70Hz, 2H), 7.28 (d, *J*= 8.70Hz, 1H), 7.20 (t, *J*= 7.10Hz, 1H), 6.90 (d, *J*=7.97 Hz, 2H), 4.68 (dd, *J*=3.30Hz, *J*=13.20Hz , 1H), 3.81 (s, 3H), 3.30 (dd, *J*=13.20Hz, *J*=16.50Hz, 1H), 3.18 (dd, *J*=3.30Hz, *J*=16.23Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 194.73, 159.66, 142.38, 133.72, 130.51, 129.28, 128.67, 127.27, 125.25, 114.39, 55.43, 47.00, 45.02.

2-(3-nitrophenyl) thiochroman-4-one MF17



Yellow solid; Mp = 112 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.14 (d, *J*=8.24 Hz 1H), 8.08 (d, *J*=8.49 Hz 1H), 7.70 (d, *J*=8.95 Hz, 1H), 7.51 (t, *J*=7.92 Hz, 1H), 7.38 (t, *J*=7.92 Hz, 1H), 7.16-7.24 (m, 2H), 4.75 (dd, *J*=3.66Hz, *J*=12.56Hz , 1H), 3.29 (dd, *J*=12.56Hz, *J*=16.22Hz, 1H), 3.19 (dd, *J*=3.66Hz, *J*=16.74Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 193.19, 148.54, 140.77, 140.55, 133.97, 133.48, 130.07, 129.94, 129.33, 127.27, 125.73, 123.46, 122.64, 46.14, 44.58.

(E)-1-(2-(3-(2-aminophenyl)-3-oxo-1-phenylpropylamino) phenyl)-3-phenylprop-2-en-1-one MF.s



Golden yellow solid; Mp = 118 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.73 (d, *J*= 6.17 Hz, 1H, NH), 7.89 (d, *J*= 6.25 Hz, 1H), 7.62-7.77 (m, 5H), 7.39-7.49 (m, 5H), 7.31 (t, *J*=8.61 Hz, 2H), 7.20-7.25 (m, 4H), 6.69 (d, *J*= 8.81 Hz, 1H), 6.60-6.63(m, 2H), 6.25 (bs, NH_2), 5.30 (dd, *J*=7.19Hz, *J*=13.87Hz, 1H), 3.59 (dd, *J*=7.19Hz, *J*=15.92Hz, 1H), 3.48 (dd, *J*=6.26Hz, *J*=15.91Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 198.83, 191.85, 150.83, 150.63, 143.00, 142.76, 134.57, 131.12, 130.09, 128.96, 128.88, 128.30, 127.36, 126.57, 115.91, 114.73, 53.43, 47.71; IR (ATR) 3470, 3344, 1638, 1569, 1513, 1198, 1159, 735, 696cm^{-1}; HRMS (ESI) calculated for $C_{30}H_{26}N_2O_2H$ $[M+H]^+$ 447.1994, found 447.2104.

Experimental procedure and spectroscopic data for chapter 8 and 9

General

All melting points were determined using a Mel-Temp II melting point instrument. Elemental analyses (C, H, N) were conducted using a PerkinElmer 2400 elemental analyzer, their results were found to be in good agreement (±0.3%) with the calculated values.NMR spectra were obtained using a Jeol ECA 400 (400 MHz) and Lambda 400. EX 270 (270MHz) NMR spectrometers with TMS as the internal standard. All chemical shifts are reported in ppm. The IR spectra were taken with a Perkin Elmer 400 ATR-FTIR spectrophotometer. The mass spectra were taken on an Agilent 1200 LC/MS. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60 F-254) using UV light (254 and 366 nm) for detection. Column chromatography was carried out with silica gel 60 (230-400 mesh) from Merck. All target compounds were characterized by ^{1}H, ^{13}C and other spectroscopy analyses. All reactions were carried out under nitrogen atmosphere unless specified. All solvents, reagents and ionic liquids were purchased from Aldrich, Merck or Fisher except for IL-A, IL-E, IL-F and IL-G which were synthesized in our labratory.

Synthesis of IL-A:

A dilute nitric acid solution (5.059 g of nitric acid (65 wt %) in 20 mL water) was added to a solution of 1.05 equiv of *N*-methylimidazol (4.089 g , 49.79 mmol) at 0 ˚C. The reaction mixture was allowed to warm to room temperature. Water was removed by passing compressed air above the solution at 80 ˚C. The mixture was cold to room temperature and white solid was separated. The resulting solid material was washed with diethyl ether and dried in vacuum at 40 ºC. IL-A was decolorized by refluxing the

aqueous solution in the presence of charcoal for 24 h. The mixture was filtered and water of filtrate was removed in vacuum for 12 h.

Synthesis of IL-F:

α,α-Dibromo-*p*-xylene and 1-butylimidazole (1:2.1) were refluxed in acetonitrile (50 ml) for 4 h. The solvent was removed under reduced pressure and the ionic liquid was dissolved in water and extracted with ethyl acetate several times. The water was removed under reduced pressure and the product was dried under vacuum at 80 °C. 85% yield, colorless solid. M.p. 165-166 ^{o}C.

Synthesis of IL-E:

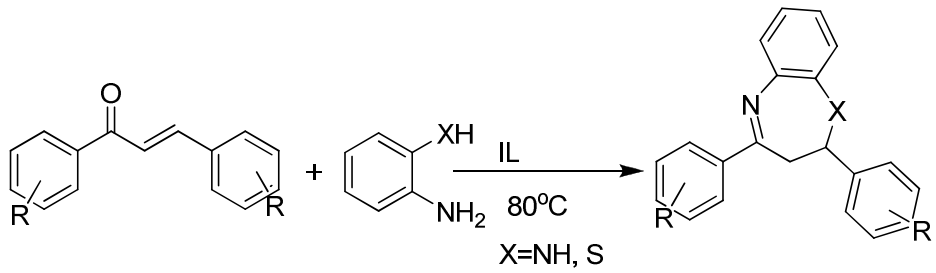
An aqueous solution of $LiN(CF_3SO_2)_2$ was added to IL-F in water (2.1:1) and stirred for 24 h. Dichloromethane was added to the solution and the ionic liquid was washed several times with aliquots of water until no longer bromide residues were detected by the $AgNO_3$ test. The product was dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. Crystals of IL-E were formed at room temperature before they were dried under vacuum for a few hours. 85% yield, colorless solid. M.p. 49-50 ^{o}C

Synthesis of IL-G:

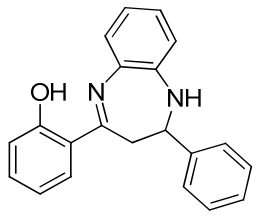
An aqueous solution of $NaCF_3SO_3$ was added to IL-F in water (2.1:1) and stirred for 24 h. The solvent was removed under reduced pressure and crystals of IL-G were formed at 4 °C and were dried under vacuum. 70% yield, colorless crystals. M.p. 92-94 ^{o}C

General procedure for preparation of 1, 5- benzodiazepine and 1, 5-benzothiazepines MA1- MA15:

A mixture of *o*-aminothiophenol (1.2 mmol) / *o*-phenylendiamine (1mmol), chalcone (1.0 mmol), and ILG (0.2 mmol, 0.1 gr per mmol of chalcone) was stirred at 80 ^{0}C for an appropriate time. The completion of reaction was followed by TLC using EtOAc in hexane as eluent. After completion, the reaction mixture was diluted with water and extracted with diethyl ether. The combined organic layer was separated, dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure to afford the 1, 5-benzothiazepines and purified by chromatography through a column of silica-gel ethyl acetate in *n*-hexane as eluent and fully characterized. The aqueous layer consisting of the IL was subjected to distillation to remove water, leaving behind the IL, which could be recycled.

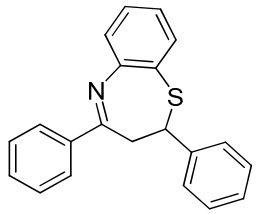


2-(2-phenyl-2, 3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)phenol MAZ



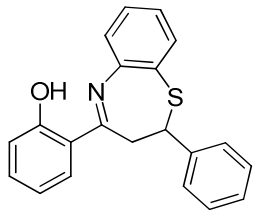
Light yellow solid; Mp = 115°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 15.28 (s, OH), 7.42-7.43 (m, 2H), 7.27-7.37 (m, 6H), 7.12(td, *J*=1.53Hz, *J*=8.26Hz, 1H), 6.99-7.05 (m, 2H), 6.85(dd, *J*=1.34Hz, *J*=7.79Hz, 1H), 6.72-6.79 (m, 1H), 5.21 (dd, *J*=3.08Hz, *J*=8.02Hz , 1H), 3.84 (bs, NH), 3.33 (dd, *J*=3.70Hz, *J*=13.58Hz, 1H), 3.06 (dd, *J*=8.64Hz, *J*=13.58Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 171.32, 162.59, 144.26, 139.04, 135.23, 132.84, 128.99, 128.34, 128.29, 128.05, 127.42, 125.88, 121.48, 120.72, 119.07, 118.30, 118.00, 69.99, 36.52.

2, 4-diphenyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA1



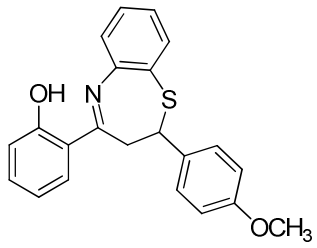
Yellow solid; Mp = 102 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.01-8.06 (m, 3H), 7.30-7.52 (m, 11H), 4.98 (dd, *J*=4.76Hz, *J*=12.70Hz , 1H), 3.31 (dd, *J*=4.69Hz, *J*=12.90Hz, 1H), 3.07 (t, *J*=12.61Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 168.67, 152.42, 144.84, 137.65, 135.04, 128.81, 128.74, 128.60, 128.48, 128.42, 128.32, 127.82, 127.29, 126.00, 121.84, 60.47, 37.63.

2-(2-phenyl-2, 3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol MA2



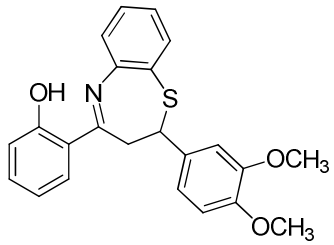
Yellow Crystal (recrystalized from ethanol); Mp = 151 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.49 (bs, OH), 7.65 (dd, *J*=1.68Hz, *J*=7.98Hz , 1H), 7.50 (dd, *J*=1.68Hz, *J*=8.51Hz , 1H), 7.49 (dt, *J*=1.05Hz, *J*=7.98Hz , 1H), 7.39-7.43 (m, 1H), 7.31-7.34 (m, 6H), 7.22 (dt, *J*=1.26Hz, *J*=8.40Hz , 1H), 7.07 (d, *J*= 8.40, 1H), 6.68-6.92(m, 1H), 5.06 (dd, *J*=4.67Hz, *J*=12.64Hz , 1H), 3.41 (dd, *J*=4.74Hz, *J*=13.27Hz, 1H), 3.09 (t, *J*=13.27Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 173.13, 162.78, 148.83, 143.68, 135.21, 133.65, 129.95, 128.89, 128.36, 128.07, 126.41, 126.04, 125.66, 124.44, 118.68, 118.59, 118.29, 60.05, 36.89; IR (ATR): 3055, 1596, 1445, 1194, 725, 737 cm^{-1}

2-(2-(4-methoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA3



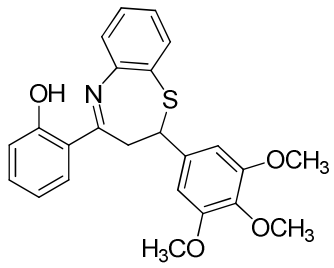
Yellow solid; Mp = 165 °C.^{1}H NMR (400MHz, $CDCl_3$): δ 14.52 (bs, OH), 7.58 (dd, *J*=1.62Hz, *J*=7.67Hz , 1H), 7.58 (dd, *J*=1.39Hz, *J*=7.91Hz , 1H), 7.48 (dt, *J*=1.62Hz, *J*=8.37Hz , 1H), 7.38-7.43 (m, 1H), 7.19-7.32 (m, 4H), 7.07 (dd, *J*=1.16Hz, *J*=8.61Hz , 1H), 6.84-6.92(m, 3H), 5.04 (dd, *J*=4.95Hz, *J*=12.11Hz , 1H), 3.80 (s, 3H), 3.38 (dd, *J*=4.95Hz, *J*=12.66Hz, 1H), 3.05 (t, *J*=12.66Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 173.12, 162.31, 159.31, 135.19, 133.59, 131.14, 129.86, 128.41, 127.20, 126.65, 126.34, 125.62, 125.48, 124.42, 118.65, 118.55, 114.15, 59.67, 55.35, 37.07.

2-(2-(3, 4-dimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA4



Yellow solid; Mp = 161-162 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.52 (bs, OH), 7.65 (d, *J* = 7.76 Hz, 1H), 7.52 (d, *J* = 8.11 Hz,1H), 7.47 (d, *J* = 8.11 Hz, 1H), 7.40 (t, *J* = 8.46 Hz, 1H), 7.32 (d, *J* = 8.11 Hz, 1H), 7.21 (dt, *J* = 1.28 Hz, *J* = 7.76 Hz, 2H), 7.07 (d, *J* = 7.76 Hz, 1H), 6.78 - 6.90 (m, , 3H), 5.05 (dd, *J* = 4.90 Hz, *J* =11.72 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.38 (dd, *J* = 4.96Hz, *J* =12.94 Hz, 1H), 3.08 (t, *J* = 12.41 Hz, 1H); ^{13}C NMR (100MHz,$CDCl_3$): δ 173.20, 162.74, 149.04, 148.82, 136.81, 135.05, 133.62, 131.59, 130.87, 129.97, 128.58, 126.28, 125.58, 124.68, 118.61, 118.13, 115.20, 110.97, 109.45, 60.17, 55.94, 55.77, 36.99; IR (ATR): 2920, 1565, 1419, 1266, 651 cm $^{-1}$; HRMS (ESI): calculated for $C_{23}H_{21}$ NO_3SH $[M+H]^+$ 392.1276, found 392.1295; CHN analysis: calculated for $C_{23}H_{21}NO_3S$: C: 70.56; H: 5.41; N: 3.58; O: 12.26; S: 8.19. Found: C: 70.42; H: 5.22; N: 3.44.

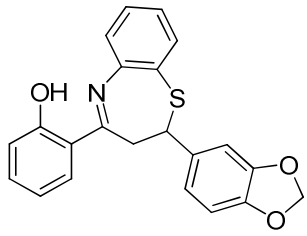
2-(2-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA5



Yellow crystal (recrystalized from 30% ethyl acetate in *n*-hezane); Mp = 160-162 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.51 (bs, OH), 7.66(d, *J* = 8.18 Hz, 1H), 7.47- 7.52 (m, 2H), 7.38-7.42 (m, 1H), 7.31(d, *J* = 8.57 Hz, 1H), 7.21(dt, *J* = 1.38 Hz, *J* = 8.36

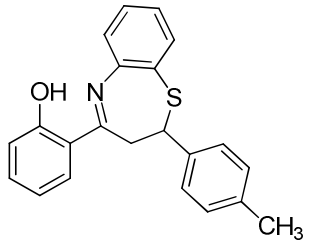
Hz,1H), 7.07 (d, J = 8.46 Hz, 1H), 6.87 (t, J = 8.18 Hz, 1H), 6.54 (s, 2H), 5.02 (dd, J = 4.67 Hz, J = 11.30 Hz, 1H), 3.83(s, 3H), 3.77(s, 6H), 3.38 (dd, J = 4.67 Hz, , J =12.86 Hz, 1H), 3.08 (t, J = 12.47 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 173.21,162.72, 153.27, 148.89, 138.80, 134.99, 133.67, 130.11, 128.62, 126.29, 125.63, 124.67, 118.63, 118.61, 118.47, 103.30, 103.28, 60.84,60.66, 56.02, 36.90; IR (ATR): 3001, 2926, 1589, 1455, 1243, 760 cm^{-1}; HRMS (ESI): calculated for $C_{24}H_{23}NO_4SH$ $[M+H]^+$ 422.1381, found 422.1391; CHN analysis: calculated for $C_{24}H_{23}NO_4S$: C: 68.39; H: 5.50; N: 3.32; O: 15.18; S: 7.61. Found: C: 68.50; H: 5.64; N: 3.18.

2-(2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA6



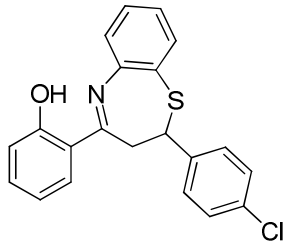
Light yellow solid; Mp = 138 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.47 (bs, OH), 7.65(dd, J = 1.25 Hz, J = 7.65 Hz, 1H), 7.58(dd, J = 1.29 Hz, J = 7.98 Hz, 1H), 7.48(dt, J = 1.33 Hz, J = 8.36 Hz, 1H), 7.38-7.41 (m, 1H), 7.31(dd, J = 1.17 Hz, J = 7.94 Hz, 1H), 7.22 (dt, J = 1.42 Hz, J = 8.36 Hz,1H), 7.07 (dd, J = 1.00 Hz, J = 8.27 Hz, 1H),6.82-6.91 (m, 1H), 6.82 (d, J = 1.33 Hz, 1H), 6.72-6.78 (m, 2H), 5.96 (s, 2H, O-CH_2-O), 5.00 (dd, J = 4.70 Hz, J = 12.18 Hz, 1H), 3.37 (dd, J = 4.98 Hz, J =13.28 Hz, 1H), 3.02 (t, J = 13.28 Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 172.95, 162.85, 148.66, 147.99, 147.31, 137.85, 135.15, 133.63, 129.93, 128.30, 126.44, 125.66, 124.31, 119.23, 118.67, 118.58, 118.23, 108.21, 106.48, 101.23, 59.95, 37.09.

2-(2-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA7



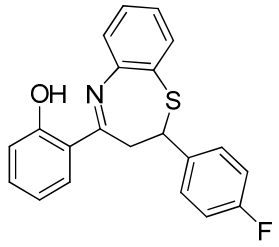
Yellow solid; Mp = 154 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.44 (bs, OH), 7.51-758 (m, 2H), 7.42 (dt, *J* = 1.55 Hz, *J* = 9.21 Hz, 1H), 7.34 (dt, *J* = 1.82 Hz, *J* = 9.48 Hz, 1H),7.22-7.25 (m, 1H), 7.09-7.14 (m, 2H), 7.07 (d, *J* = 7.85 Hz, 2H), 7.00 (d, *J* = 7.85 Hz,1H), 6.81-6.86 (m, 1H), 4.95 (dd, *J* = 4.58 Hz, *J* = 12.43 Hz, 1H), 3.29 (dd, *J* = 4.58 Hz, *J* =12.43 Hz, 1H), 3.00 (t, *J* = 12.43 Hz, 1H),2.27 (s, 3H) ;^{13}C NMR (100MHz, $CDCl_3$): δ 173.20, 162.73, 148.86, 141.00, 137.95, 135.30, 133.71, 130.11, 129.60, 128.39, 126.22, 125.97, 124.53, 123.14, 121.72, 118.73, 118.59, 59.95, 36.96, 21.16.

2-(2-(4-chlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA8



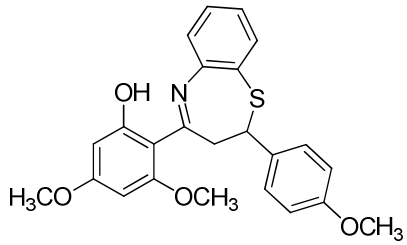
Yellow solid; Mp = 162 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.42 (bs, OH), 7.63 (dd, *J* = 1.94 Hz, *J* = 8.05 Hz, 1H), 7.55 (dd, *J* = 1.66 Hz, *J* = 8.60 Hz, 1H), 7.50 (dt, *J* = 1.66 Hz, *J* = 8.87 Hz, 1H), 7.40-7.44 (m, 1H), 7.29-7.33 (m, 4H), 7.20-7.24 (m, 2H), 7.08 (d, *J* = 7.60 Hz, 1H), 6.89-6.3 (m, 1H), 5.02 (dd, *J* = 4.94 Hz, *J* = 12.20 Hz, 1H), 3.38 (dd, *J* = 4.71 Hz, *J* =13.04Hz, 1H), 3.04 (t, *J* = 12.76 Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 172.93, 162.95, 148.85, 142.18, 135.09, 133.83, 130.16, 129.11, 128.42, 127.53, 126.69, 126.25, 125.72, 123.44, 121.14, 118.75, 118.63, 59.29, 36.89.

2-(2-(4-fluorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA9



Yellow solid; Mp = 152 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 14.45 (bs, OH), 7.66 (d, *J* = 7.77 Hz, 1H), 7.57 (d, *J* = 7.77 Hz, 1H), 7.51 (dt, *J* = 1.29 Hz, *J* = 7.77 Hz, 1H), 7.42 (dt, *J* = 1.29 Hz, *J* = 8.03 Hz, 1H), 7.29-7.38 (m, 4H), 7.09 (d, *J* = 7.78 Hz, 1H), 7.02 (t, *J*= 8.29, 2H), 6.92 (t, *J*= 7.51, 1H), 5.05 (dd, *J* = 4.41 Hz, *J* = 11.92 Hz, 1H), 3.41 (dd, *J* = 4.66 Hz, *J* =12.95Hz, 1H), 3.05 (t, *J* = 12.44 Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 172.94, 163.13, 149.00, 134.72, 133.71,133.14, 130.14, 128.36, 127.98, 127.45, 126.70, 126.06, 124.42, 124.32, 118.81, 118.45, 115.75, 59.33, 36.91.

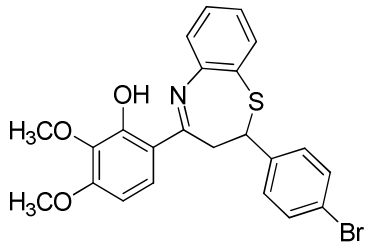
3, 5-dimethoxy-2-(2-(4-methoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA10



Yellow solid; Mp = 168-170 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 16.82 (bs, OH), 7.64 (d, *J* = 8.19 Hz, 1H), 7.45 (d, *J* = 7.56 Hz, 1H), 7.45 (t, *J* = 7.56 Hz, 1H), 7.16-7.31 (m, 4H), 6.85 (d, *J* = 8.83 Hz, 2H), 6.17 (d, *J* = 1.89 Hz, 1H), 5.96 (d, *J* = 1.89 Hz, 1H), 5.20 (dd, *J* = 4.41 Hz, *J* = 12.93 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.62 (dd, *J* = 4.73 Hz, *J* =12.29Hz, 1H), 2.89 (t, *J* = 12.29 Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 172.14, 168.42, 164.23, 161.65, 158.90, 147.28, 137.25, 135.29,

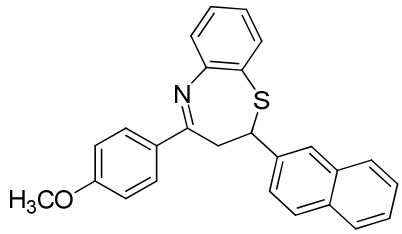
129.79, 127.12, 126.14, 126.02, 125.63, 114.15, 103.71, 94.72, 90.55, 59.13, 55.66, 55.54, 55.39, 41.90; HRMS (ESI): calculated for $C_{24}H_{23}NO_4SH$ $[M+H]^+$ 422.1381, found 422.1973.

6-(2-(4-bromophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)-2,3-dimethoxyphenol MA11



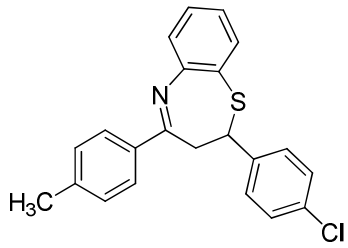
Yellow solid; Mp =156-157 °C. ^{1}H NMR (270MHz, $CDCl_3$): δ 14.40 (bs, OH), 7.60 (dd, *J* = 1.05 Hz, *J* = 7.62 Hz, 1H), 7.48 (dd, *J* = 1.27 Hz, *J* = 7.62 Hz, 1H), 7.46 (d, *J* = 8.47 Hz, 2H), 7.18-7.30 (m, 5H), 6.50 (d, *J* = 8.89 Hz, 1H), 4.97 (dd, *J* = 4.87 Hz, *J* = 12.49 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.31 (dd, *J* = 4.66 Hz, *J* =13.13Hz, 1H), 3.02 (t, *J* = 12.71 Hz, 1H);^{13}C NMR (67.5MHz, $CDCl_3$): δ172.34, 157.60, 156.62, 148.70, 142.56, 137.19, 135.08, 131.98, 130.17,127.78, 126.29, 125.67, 124.09, 123.97, 121.78, 113.44, 102.52, 60.60, 59.16, 56.04, 36.64 ; IR (ATR): 2927, 1605, 1556,1449, 1289, 1076, 783, 702 cm^{-1}; HRMS (ESI): calculated for $C_{23}H_{20}BrNO_3S$ H $[M+H]^+$ 470.0350, found 470.0454; CHN analysis: calculated for $C_{23}H_{20}BrNO_3S$: C: 58.73; H: 4.29; Br: 16.99; N: 2.98; S: 6.82. Found: C: 58.81; H: 4.35; N: 2.84.

4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepine MA12



Yellow crystal (recrystalized from 20% ethyl acetate in *n*-hezane); Mp = 128-130 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.06 (d, *J*=8.79 Hz , 2H),7.76-7.89 (m, 3H), 7.67 (s, 1H), 7.63 (d, *J*=7.88 Hz, 1H), 7.42-7.51 (m, 4H), 7.32 (d, *J*=8.19 Hz , 1H), 7.14 (t, *J*=8.19 Hz , 1H), 7.01 (d, *J*=8.79 Hz, 2H), 5.13 (dd, *J*=4.85 Hz , *J*=12.43 Hz , 1H), 3.88 (s, 3H), 3.34 (dd, *J*=4.85Hz, *J*=12.74Hz, 1H), 3.18 (t, *J*=12.43Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 168.24, 162.21, 152.77, 141.23, 135.18, 132.85, 132.19, 131.18, 129.88, 129.29, 128.94, 128.04, 127.78, 127.15, 126.49, 126.17, 125.49, 125.13, 124.54, 124.29, 114.19, 60.66, 55.57, 37.23; IR (ATR): 3051, 2929, 1592, 1235, 751 cm $^{-1}$; HRMS (ESI): calculated for $C_{26}H_{21}NOSH$ $[M+H]^+$ 396.1377, found 396.1473.

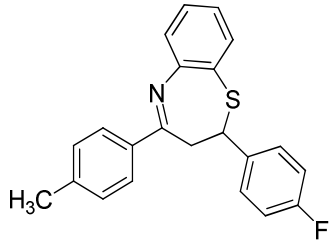
2-(4-chlorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA13



Light yellow solid; Mp = 119-121 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.93 (d, *J*=8.05Hz, 2H), 7.58 (d, *J*=7.24Hz, 1H), 7.46 (t, *J*=7.65Hz, 1H), 7.22-7.30(m, 7H), 7.13 (t, *J*=8.05Hz, 1H), 4.93 (dd, *J*=4.00Hz, *J*=12.50Hz , 1H), 3.27 (dd, *J*=4.00Hz, *J*=13.15Hz, 1H), 3.00 (t, *J*=12.58Hz, 1H), 2.43 (s, 3H, CH_3);^{13}C NMR (100MHz, $CDCl_3$): δ 168.53, 152.55, 142.63, 141.60, 135.00, 134.98, 133.43, 129.89, 129.53, 128.90, 127.45, 127.39,125.42, 125.37, 122.39, 59.65, 37.36, 21.47; IR (ATR): 2919, 1600, 1565, 1452, 1246, 749 cm $^{-1}$; HRMS (ESI): calculated for $C_{22}H_{18}ClNS$ H

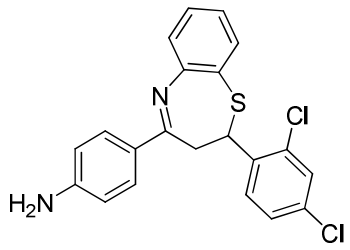
$[M+H]^+$ 364.0921, found 364.0914; CHN analysis: calculated for $C_{22}H_{18}ClNS$: C: 72.61; H: 4.99; Cl: 9.74; N: 3.85; S : 8.81. Found: C: 72.73; H: 4.86: N, 3.97.

2-(4-fluorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA14



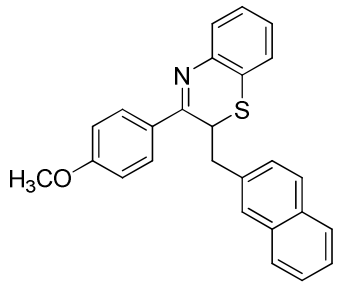
Light yellow solid; Mp = 118-119 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.93 (d, *J*=7.81Hz, 2H), 7.59 (d, *J*=7.48Hz, 1H), 7.46 (t, *J*=7.81Hz, 1H), 7.24-7.34(m, 5H), 7.13 (t, *J*=7.81Hz, 1H),6.98 (t, *J*=8.46Hz, 2H), 4.95 (dd, *J*=4.49Hz, *J*=12.34Hz ,1H), 3.26 (dd, *J*=3.92Hz, *J*=12.34Hz, 1H), 3.00 (t, *J*=12.90Hz, 1H), 2.43 (s, 3H, CH_3) ;^{13}C NMR (100MHz, $CDCl_3$): δ 168.60, 163.36, 160.95, 152.55, 141.60, 140.16, 134.97, 129.82, 129.50, 127.75, 127.38, 125.16, 122.53, 115.66, 115.45, 59.68, 37.67, 21.48; IR (ATR): 2891, 1600, 1580, 1505, 1450, 1212,744 cm $^{-1}$; HRMS (ESI): calculated for $C_{22}H_{18}FNSH$ $[M+H]^+$ 348.1217, found 348.1232; CHN analysis: calculated for $C_{22}H_{18}FNS$: C: 76.05; H: 5.22; F: 5.47; N: 4.03; S: 9.23. Found: C: 76.17; H: 5.13; N: 4.14.

4-(2-(2, 4-dichlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)aniline MA15



Pale yellow solid; Mp = 179-181 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.97 (d, *J*=8.51Hz, 2H), 7.59-7.67 (m, 2H), 7.45 (dt, *J*=1.85Hz, *J*=8.88Hz, 1H), 7.38 (d, *J*=1.85Hz, 1H), 7.28 (s, 1H), 7.20 (dd, *J*=1.48Hz, *J*=8.51Hz, 1H),7.10 (dt, *J*=1.48Hz, *J*=8.14Hz, 1H), 6.74 (d, *J*=8.81Hz, 2H), 5.43 (dd, *J*=4.40Hz, *J*=12.58Hz ,1H), 4.02 (bs, NH_2), 3.27 (dd, *J*=4.81Hz, *J*=12.95Hz, 1H), 2.78 (t, *J*=12.95Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 167.61, 153.09, 149.51, 140.15, 134.94,131.83, 129.96, 129.27, 129.05, 128.97, 128.12, 127.71, 127.41, 125.50, 124.78, 122.20, 114.59, 55.32, 35.72; IR (ATR): 3315, 3060, 1626, 1550, 1450, 1240, 735 cm^{-1} ; HRMS (ESI): calculated for C $_{21}H_{16}Cl_2N_2S$ H $[M+H]^+$ 399.0484, found 399.0524; CHN analysis: calculated for C $_{21}H_{16}Cl_2N_2S$: C: 63.16; H: 4.04; Cl: 17.76; N: 7.01; S: 8.03. Found: C: 63.23; H: 4.25; N: 7.28.

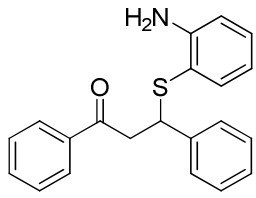
3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine (6MR)



Golden yellow crystal (recrystalized from 5% ethyl acetate in *n*-hexane); Mp = 157-158 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.95 (d, *J*=8.34 Hz , 2H), 7.74-7.83 (m, 3H), 7.57 (t, *J*=8.34 Hz, 2H), 7.39-7.47 (m, 3H), 7.28-7.33 (m, 2H), 7.17-7.21 (m, 1H), 6.93 (d, *J*=8.34 Hz , 2H), 4.26 (dd, *J*=4.94 Hz , *J*=9.27 Hz, 1H), 3.83 (s, 3H, OCH_3), 3.60 (dd, *J*=4.63Hz, *J*=13.60Hz, 1H), 2.83 (dd, *J*=9.89Hz, *J*=13.91Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ^{13}C NMR (100MHz, $CDCl_3$): δ 161.80, 158.33, 143.07, 134.87, 133.36, 132.37,129.85, 129.73, 129.24, 128.92, 128.45, 128.28, 127.99, 127.68, 127.32, 126.61, 126.52, 126.06, 125.61, 119.84, 114.04, 55.42, 37.21, 35.79; IR (ATR):

3053, 2935, 1561, 1507, 1249, 751 cm $^{-1}$; HRMS (ESI): calculated for $C_{26}H_{21}NOSH$ $[M+H]^+$ 396.1377, found 396.1982.

3-(2-aminophenylthio)-1,3-diphenylpropan-1-one; Michael adduct



Colorless crystal (recrystalized from ethanol); Mp = 107-108 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.88 (d, *J*=8.29Hz, 2H), 7.51-7.55 (m, 1H), 7.42 (t, *J*=8.78 Hz, 1H), 7.12-7.26 (m, 5H), 7.06 (d, *J*=8.78Hz, 2H), 6.66 (d, *J*=8.29Hz, 1H), 6.52 (t, *J*=7.80Hz, 1H), 4.74 (t, *J*=6.73Hz , 1H), 4.43 (bs, NH_2), 3.64 (dd, *J*=7.31Hz, *J*=17.54Hz, 1H), 3.56 (dd, *J*=6.95Hz, *J*=17.62Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$): δ 197.15, 149.47, 141.61, 137.66, 136.73, 133.23, 130.63, 129.29, 128.36, 128.06, 127.61, 127.26, 117.98, 115.69, 114.81, 47.07, 44.03; IR (ATR):3449, 3352, 1679, 1600, 1477, 744 cm $^{-1}$; HRMS (ESI): calculated for $C_{21}H_{19}NOSH$ $[M+H]^+$ 334.1221, found 334.1356.

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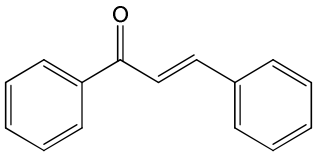
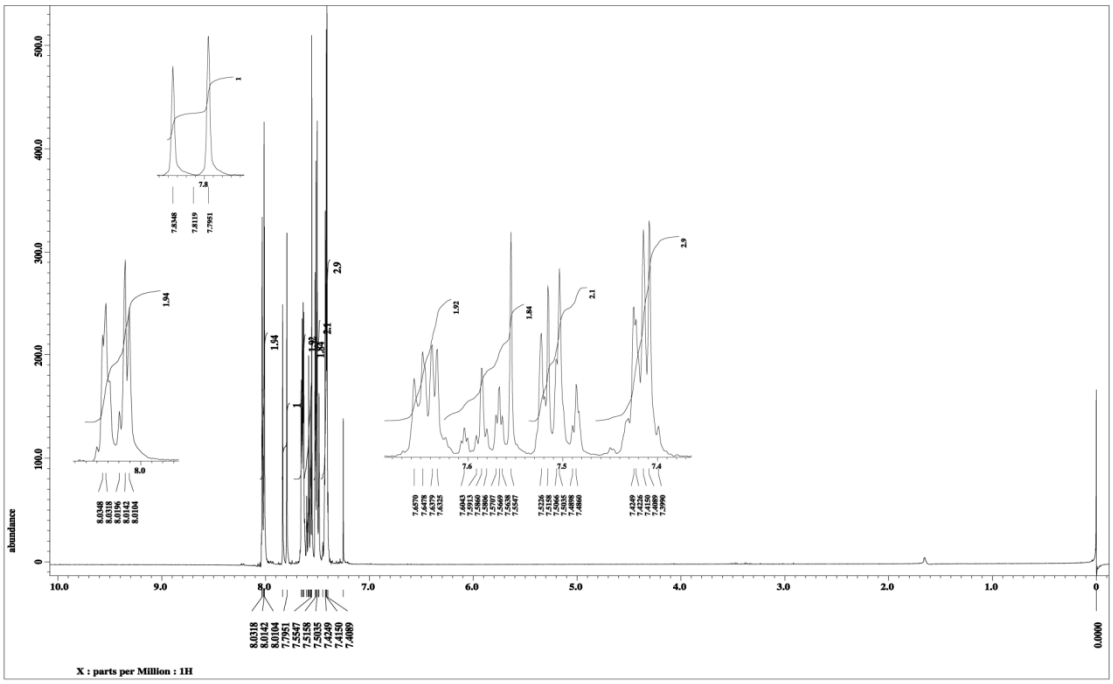
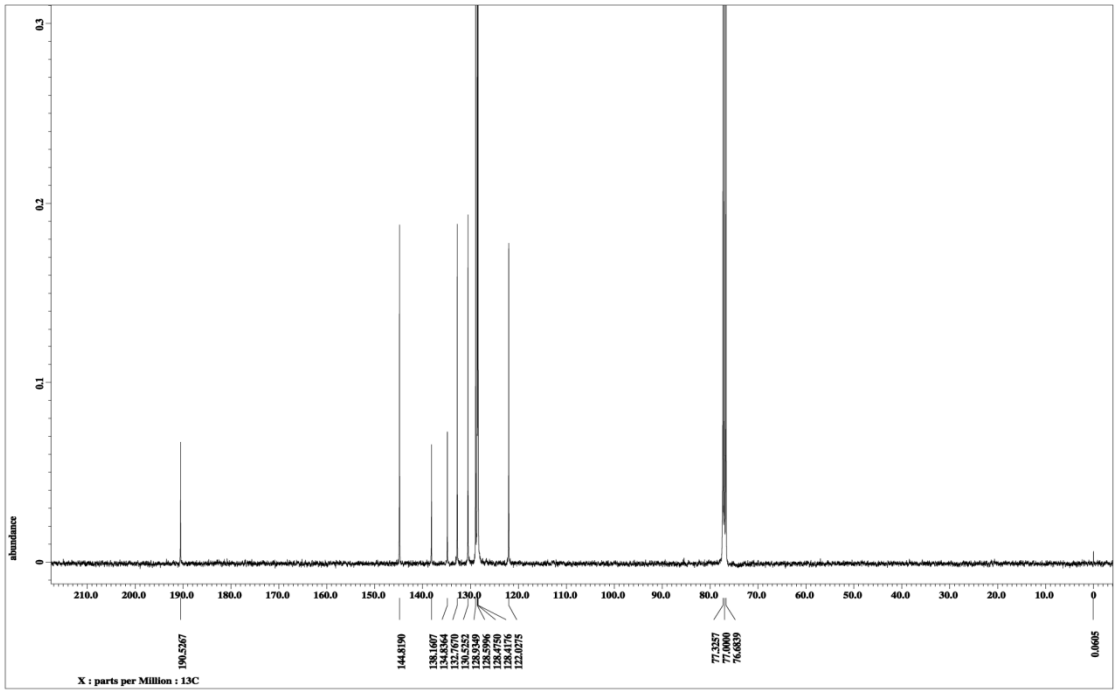
APPENDIX A

SUPPLIMENTARY DATA OF CHAPTER 4 AND 5

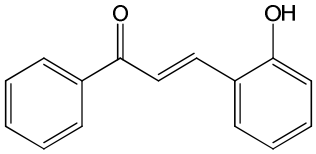
^{1}HNMR and ^{13}CNMR of 1, 3-Diphenyl-2-propen-1-one (*E*-chalcone) MC1

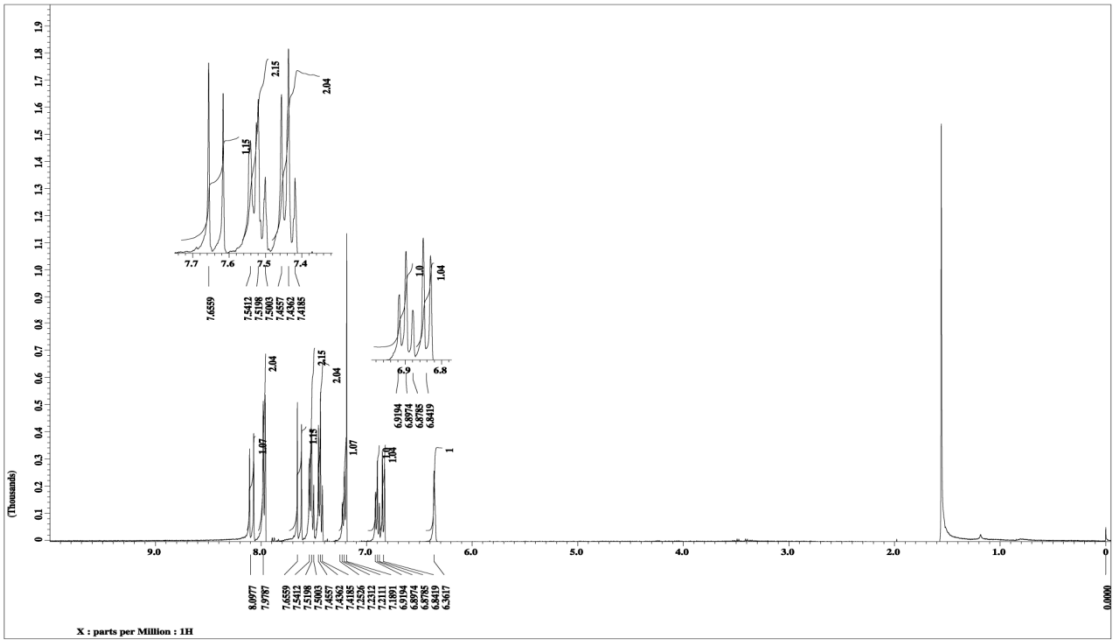


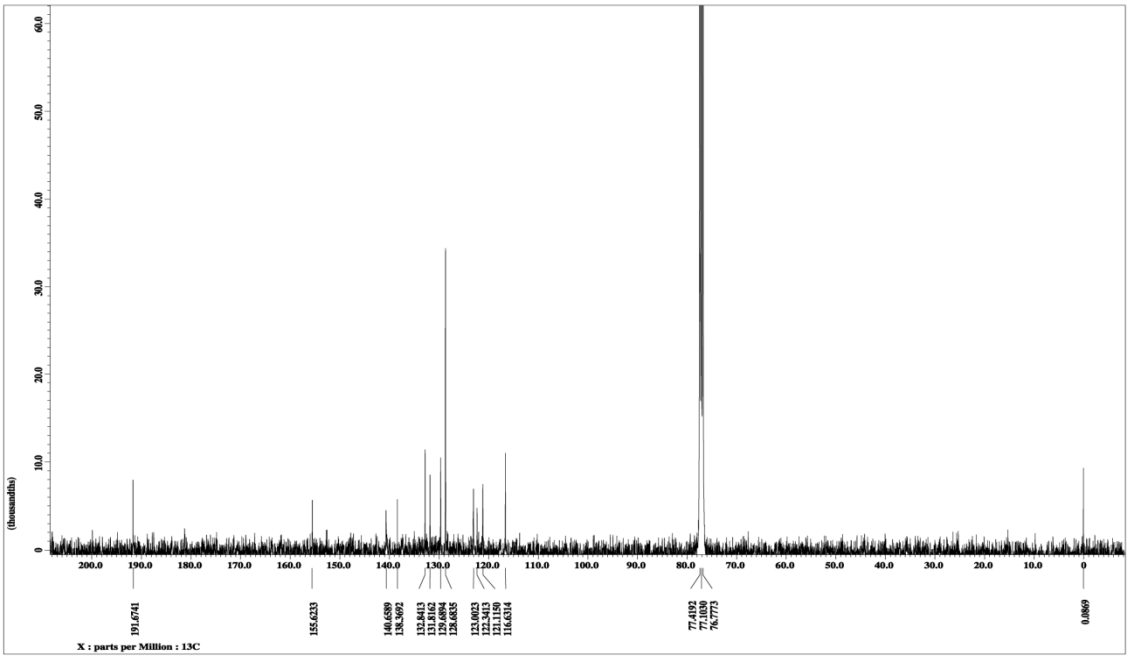




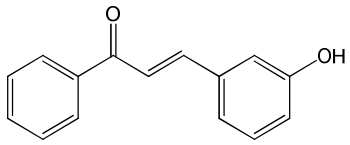
^{1}HNMR and ^{13}CNMR of (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one MC2

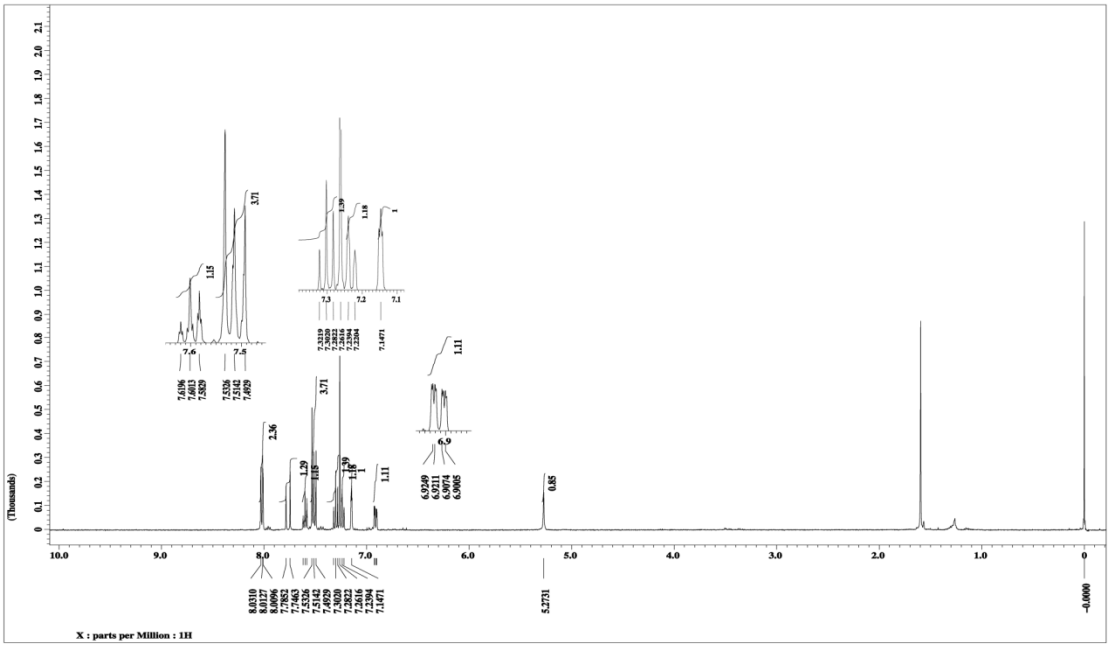


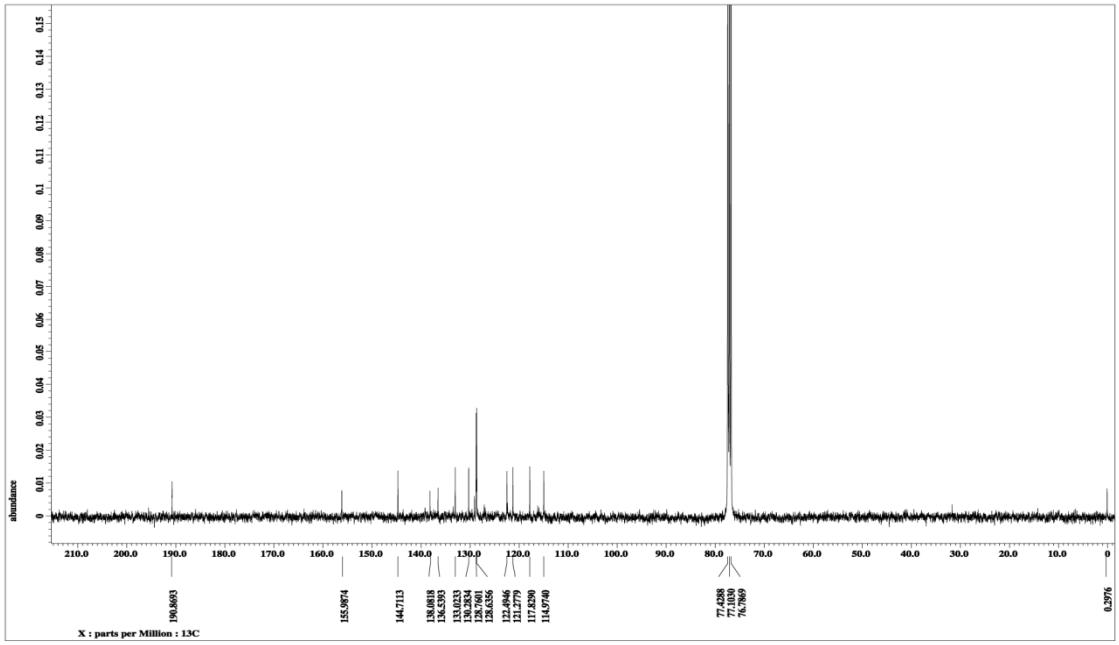




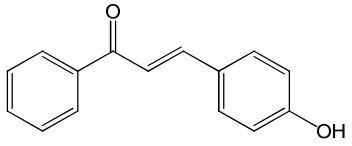
^{1}HNMR and ^{13}CNMR of (*E*)-3-(3-hydroxyphenyl)-1-phenylprop-2-en-1-one MC3

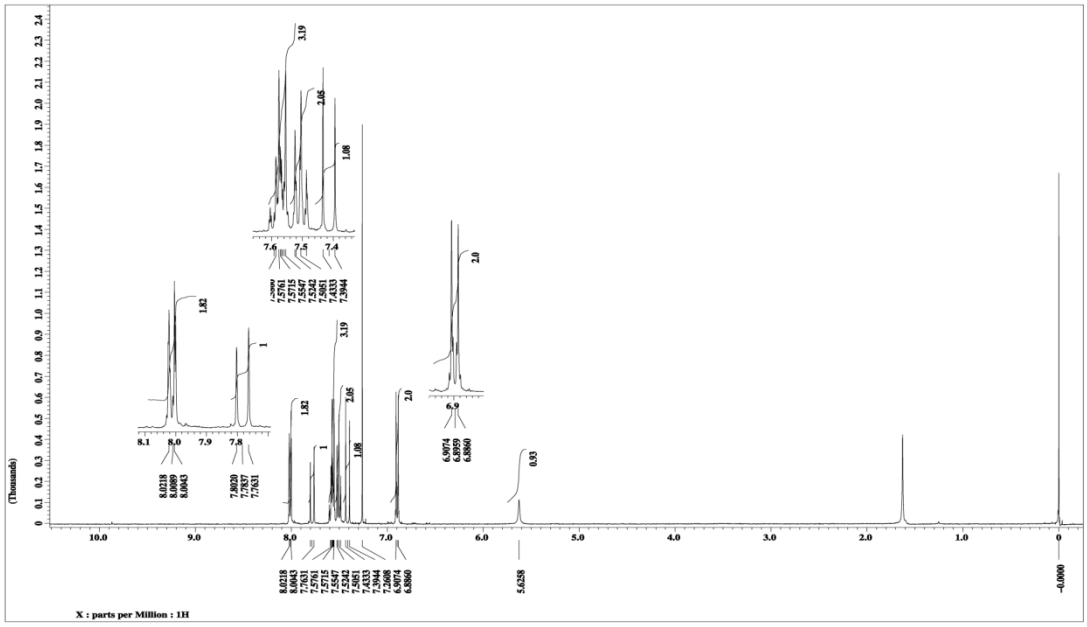


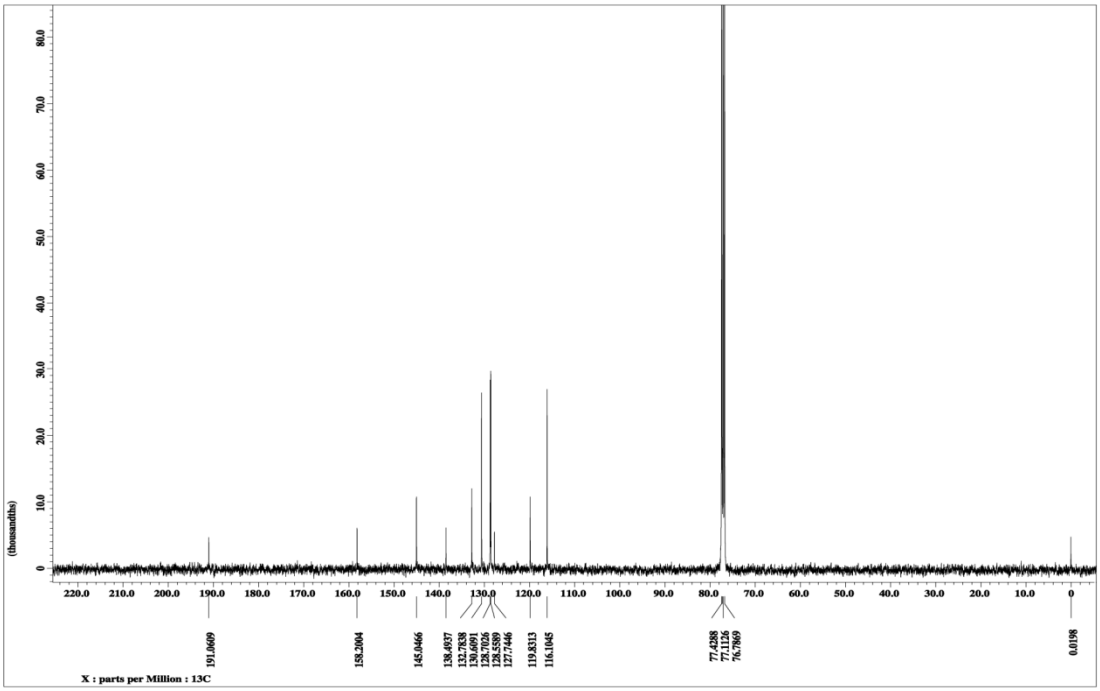




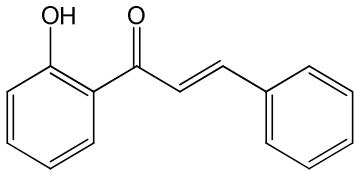
[1]HNMR and [13]CNMR of (*E*)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one MC4

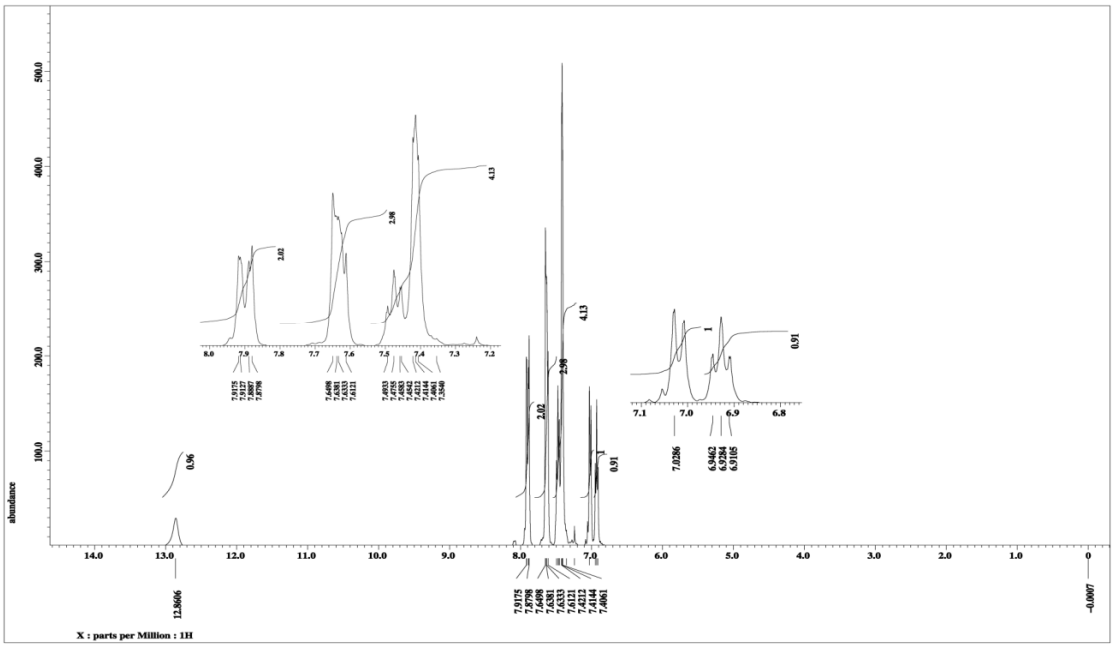


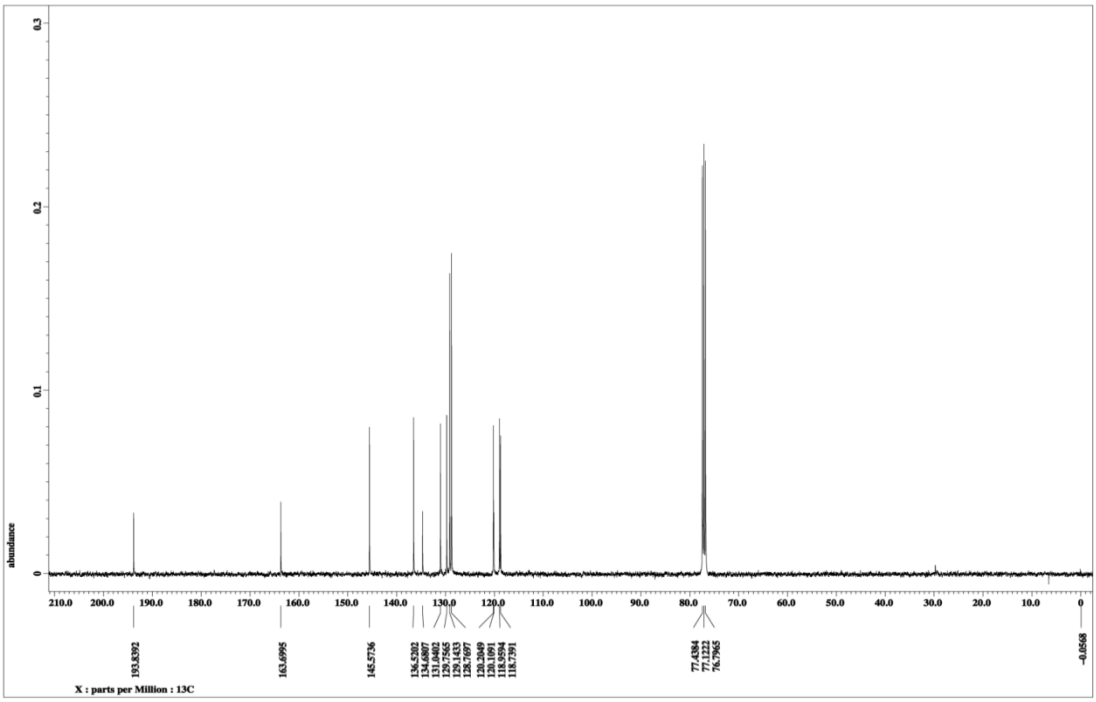




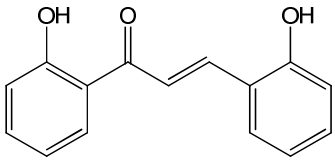
[1]HNMR and [13]CNMR of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one MC5

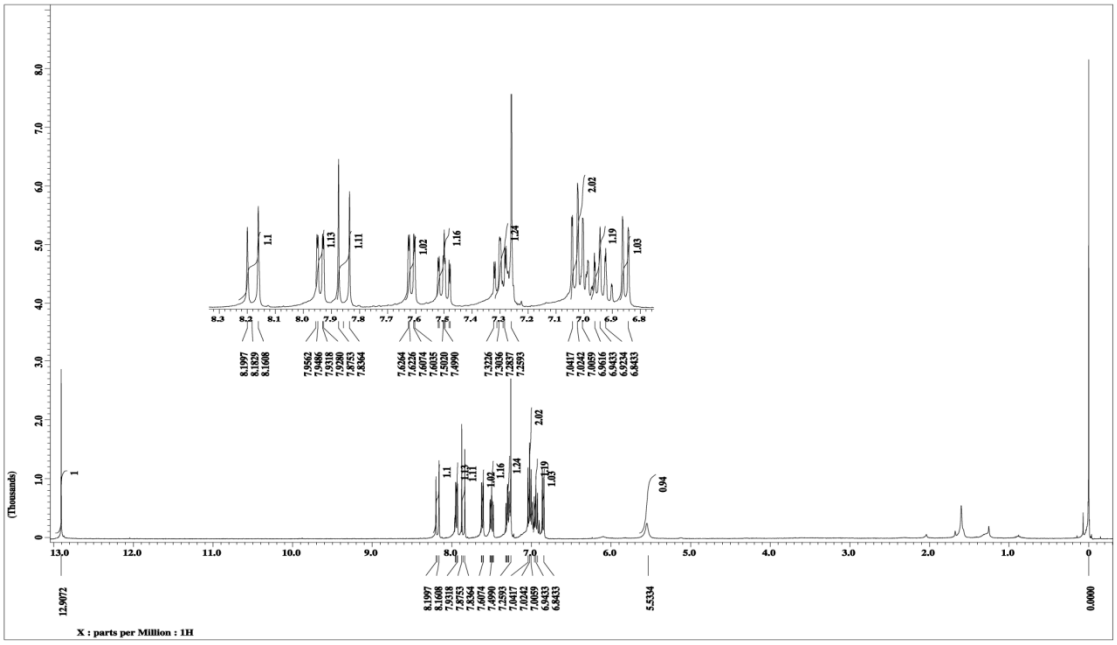


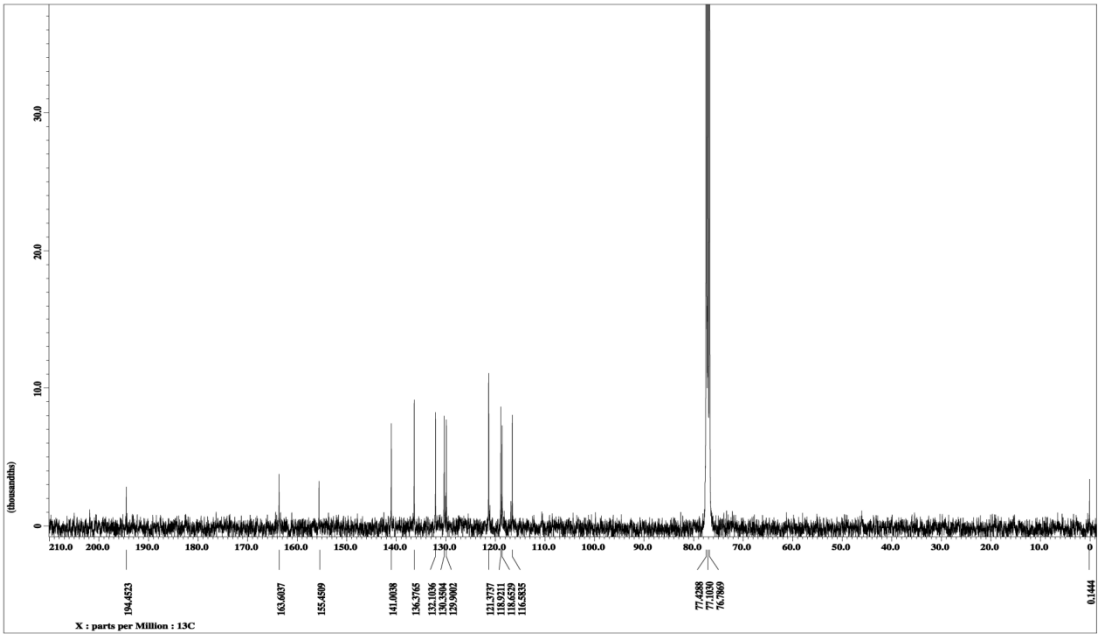




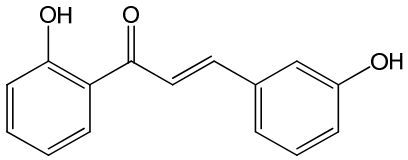
^{1}HNMR and ^{13}CNMR of (*E*)-1, 3-bis (2-hydroxyphenyl) prop-2-en-1-one MC6

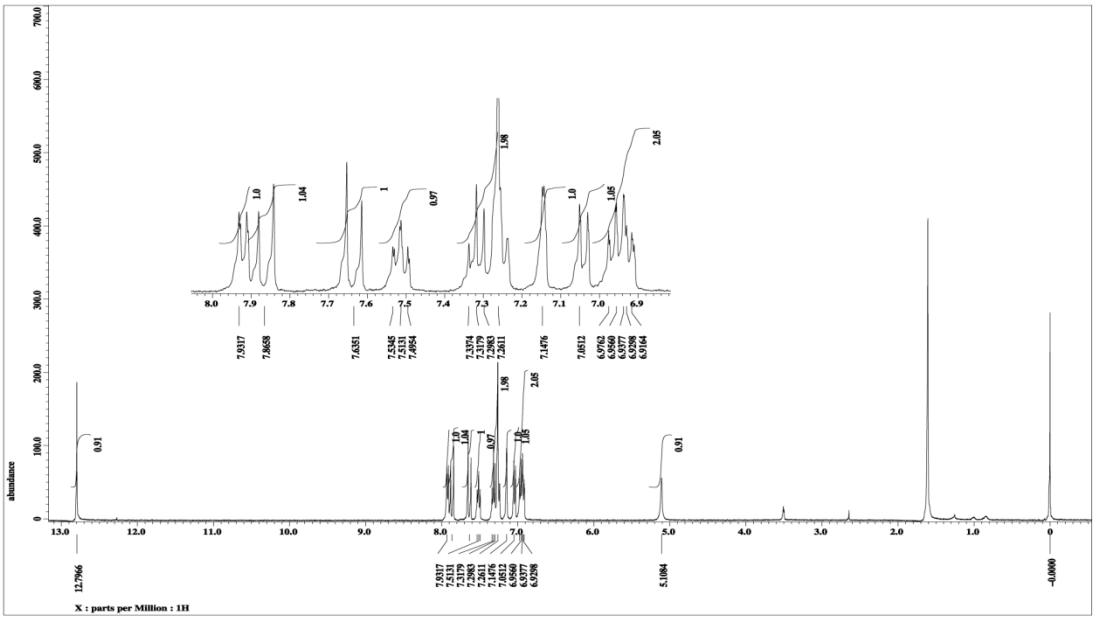


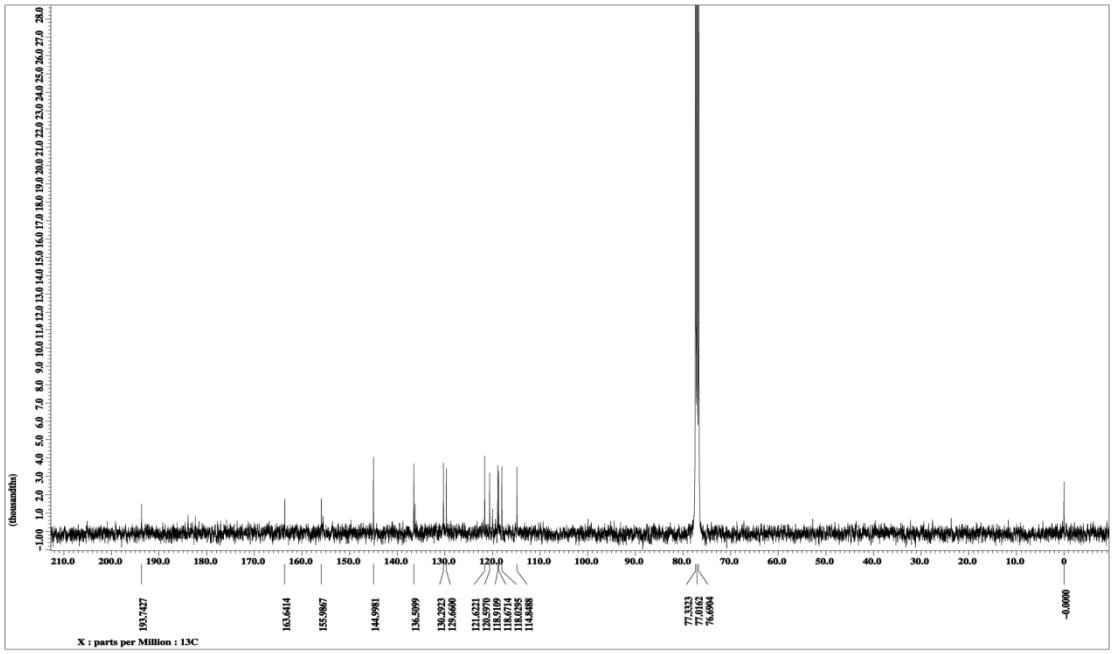




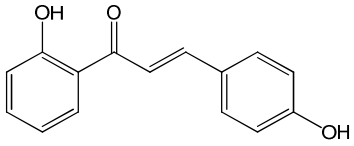
[1]HNMR and [13]CNMR of (*E*)-1-(2-hydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one MC7

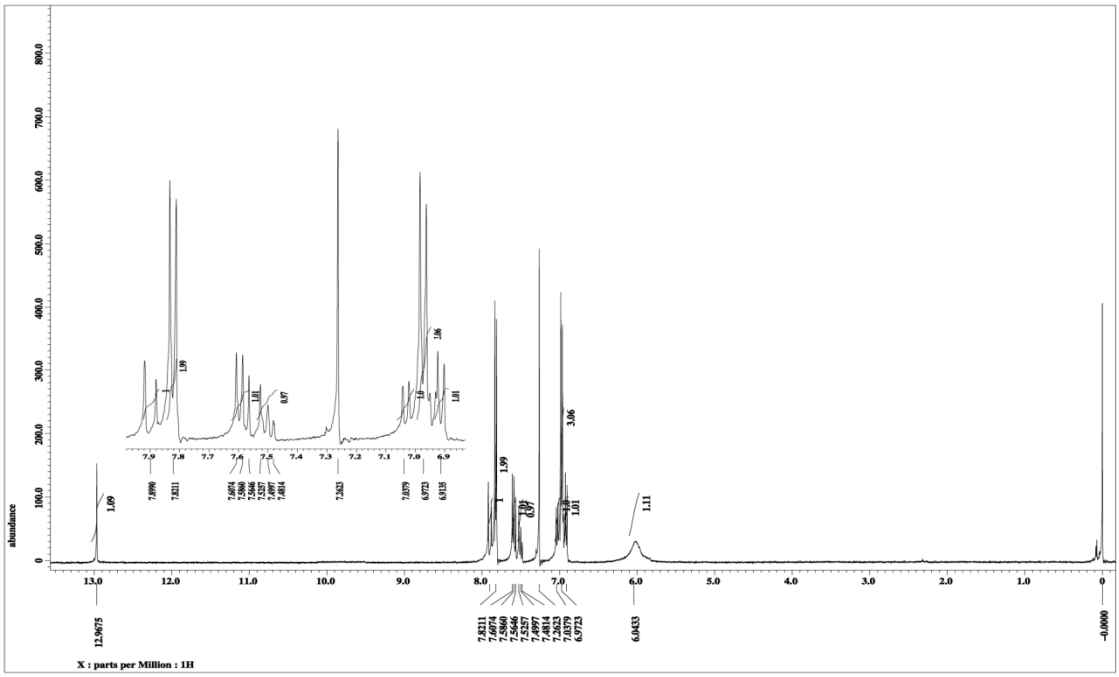


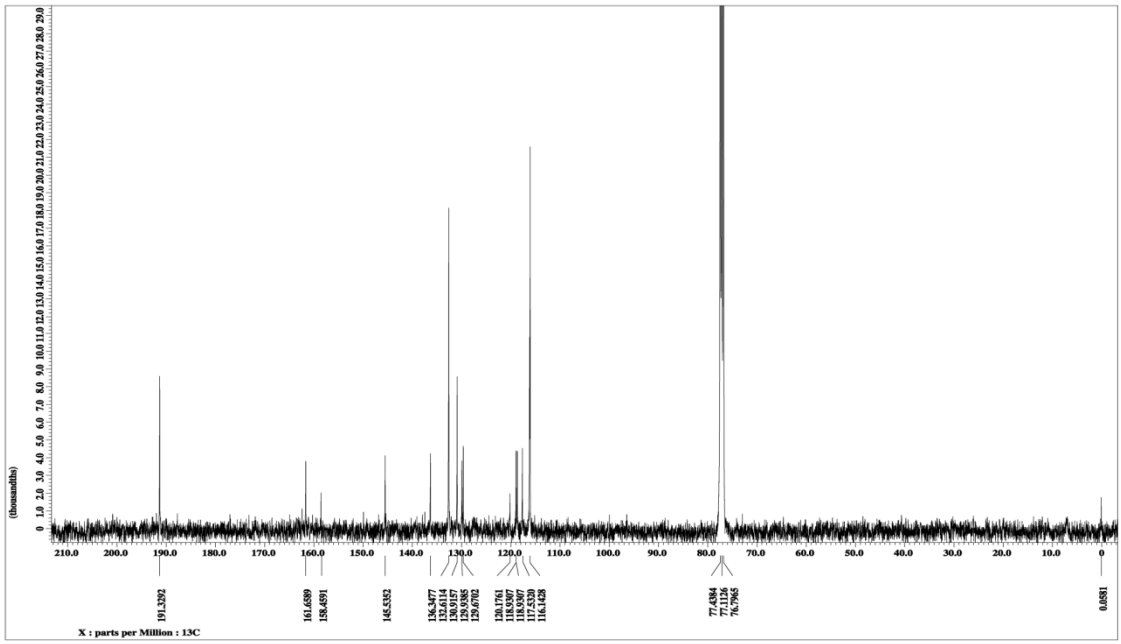




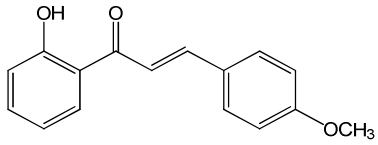
[1]HNMR and [13]CNMR of (*E*)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one MC8

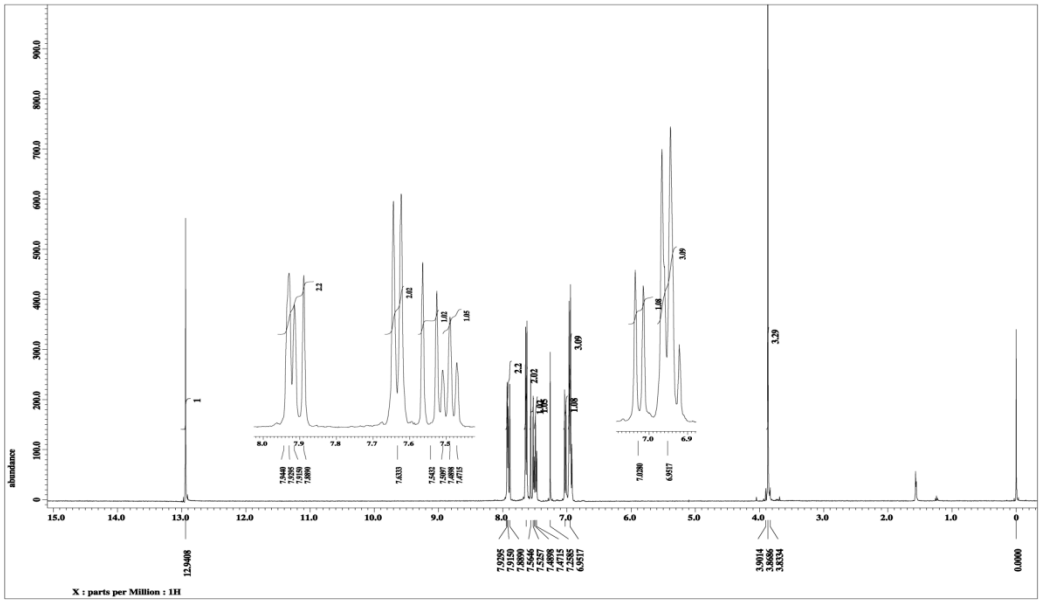


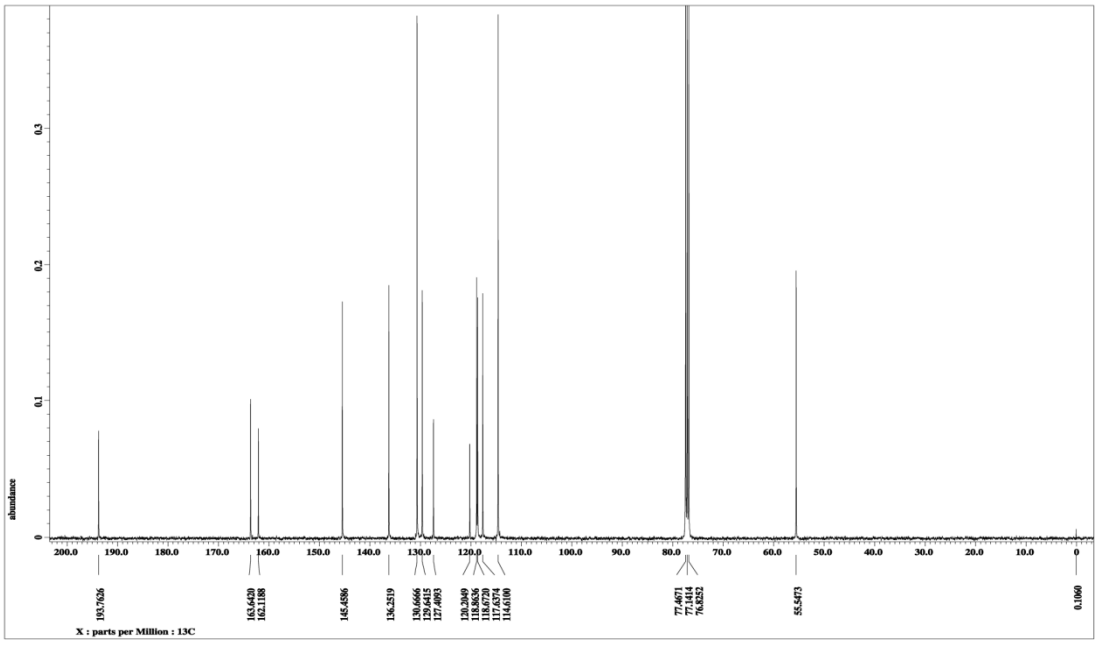




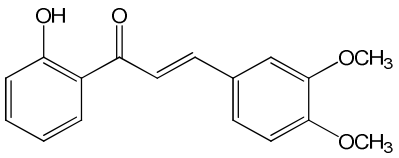
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one MC9

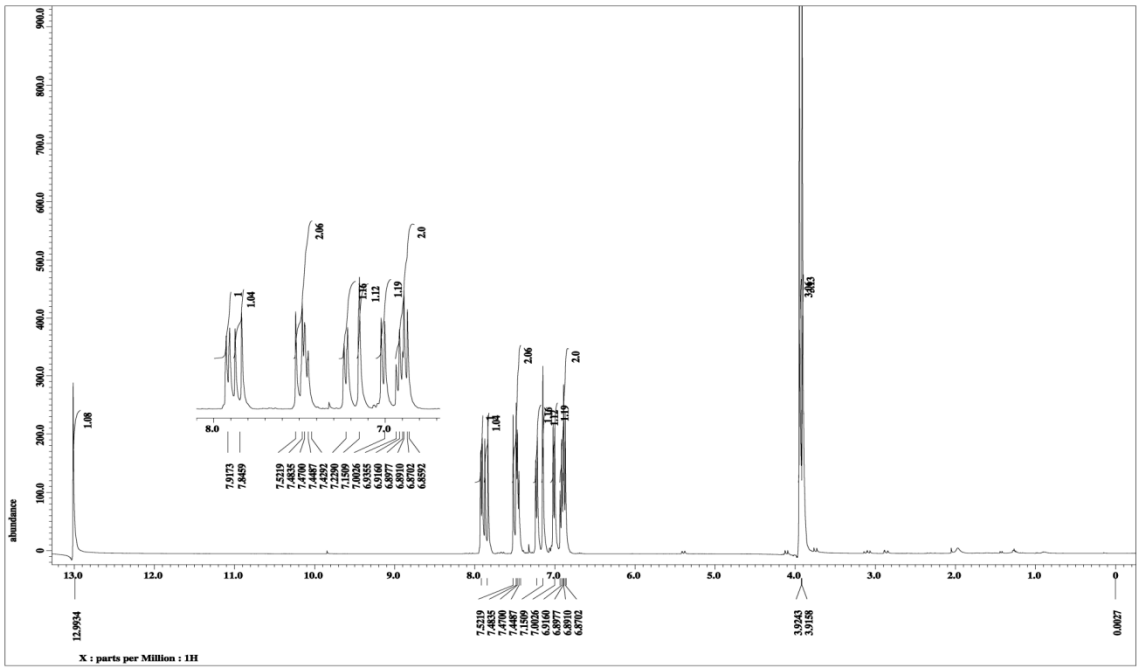


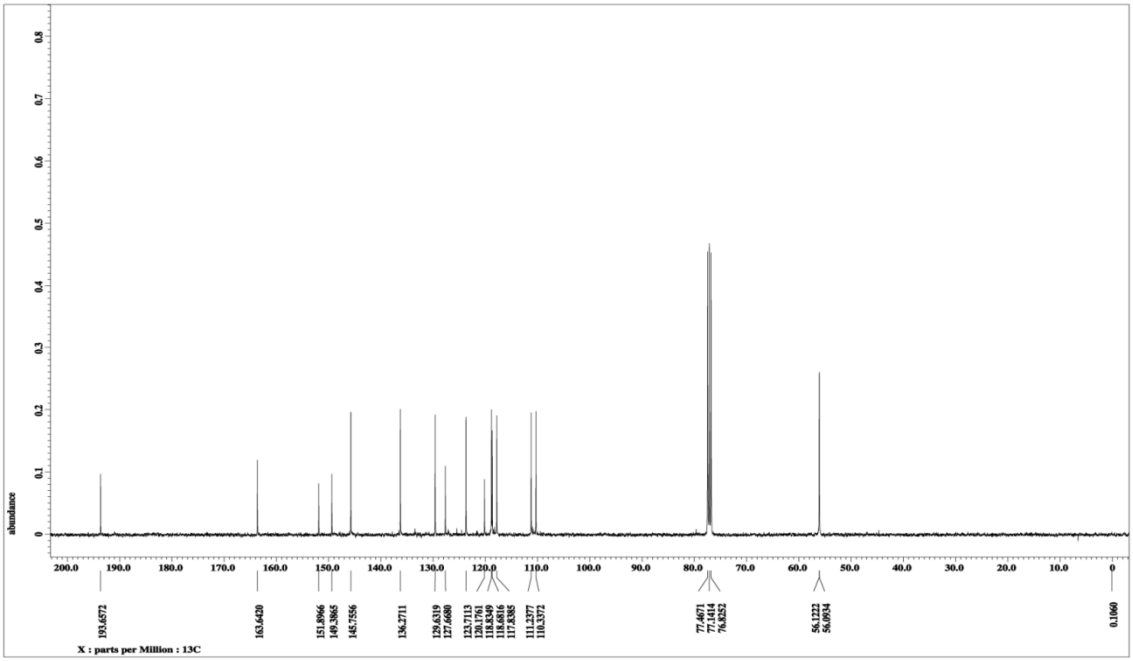




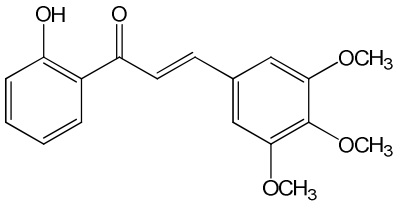
^{1}HNMR and ^{13}CNMR of (*E*)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one MC10

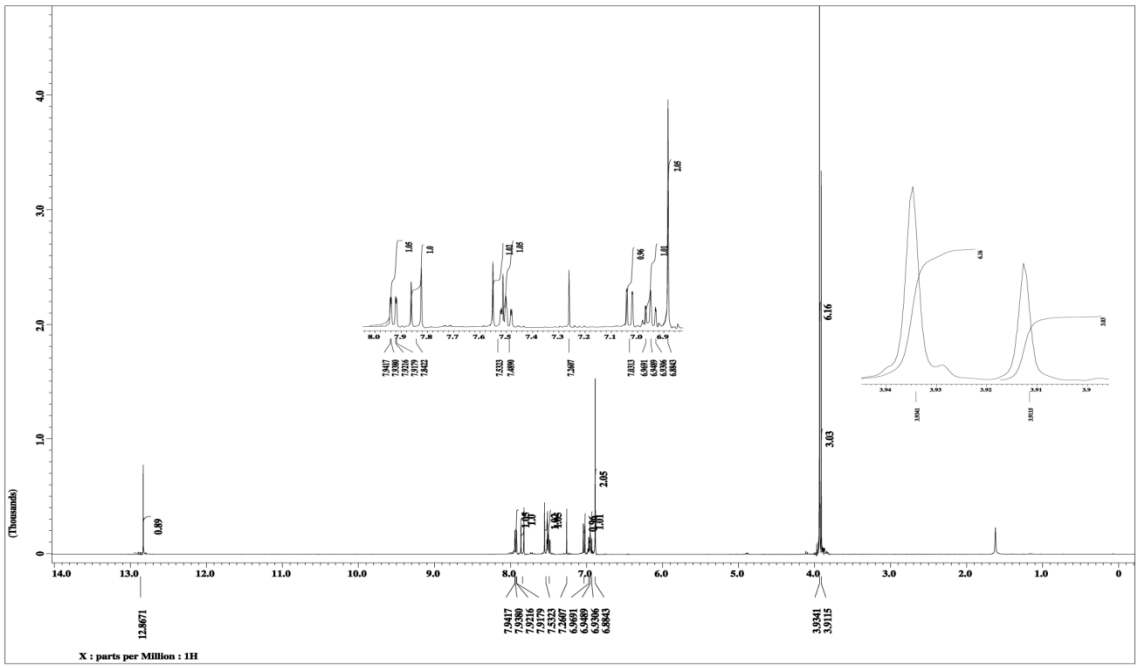


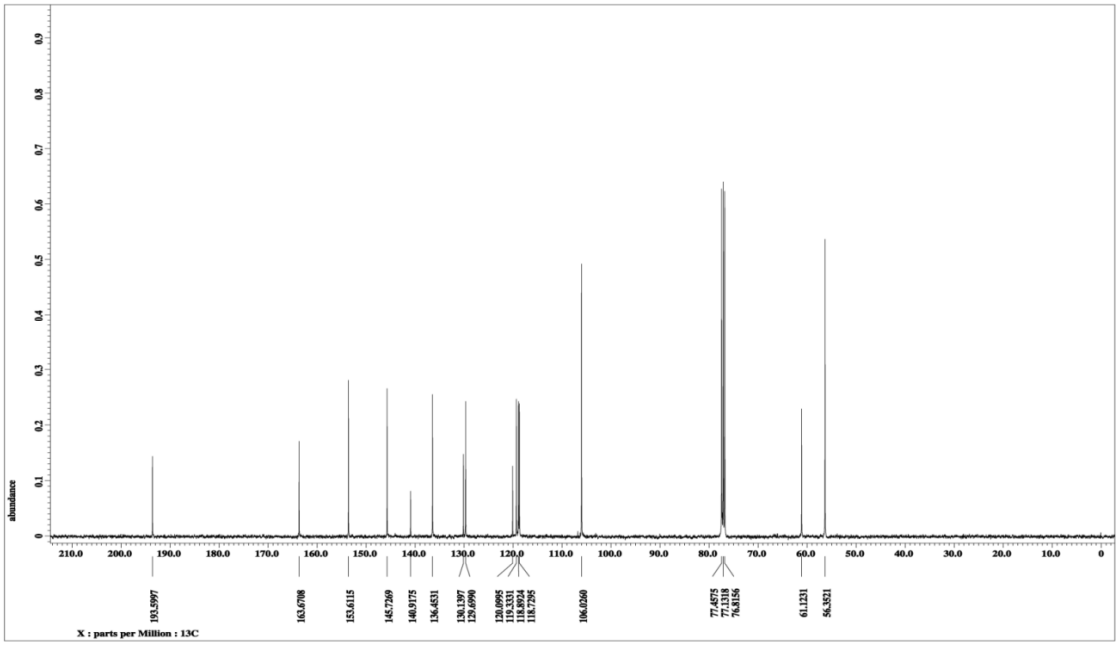




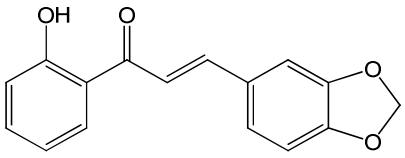
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one MC11

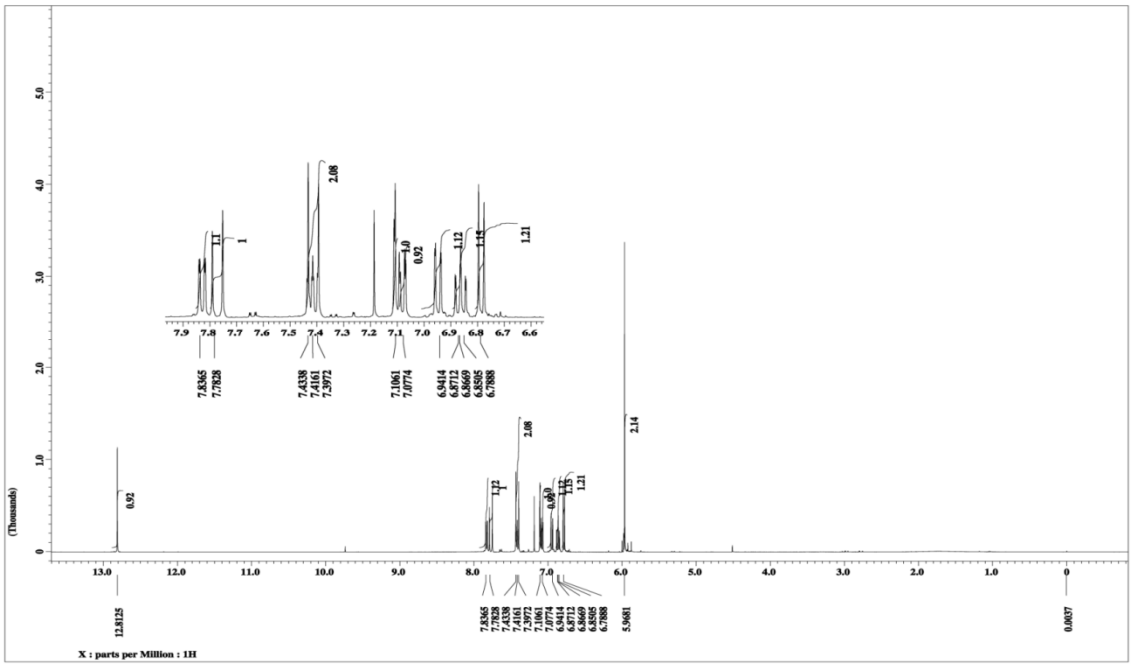


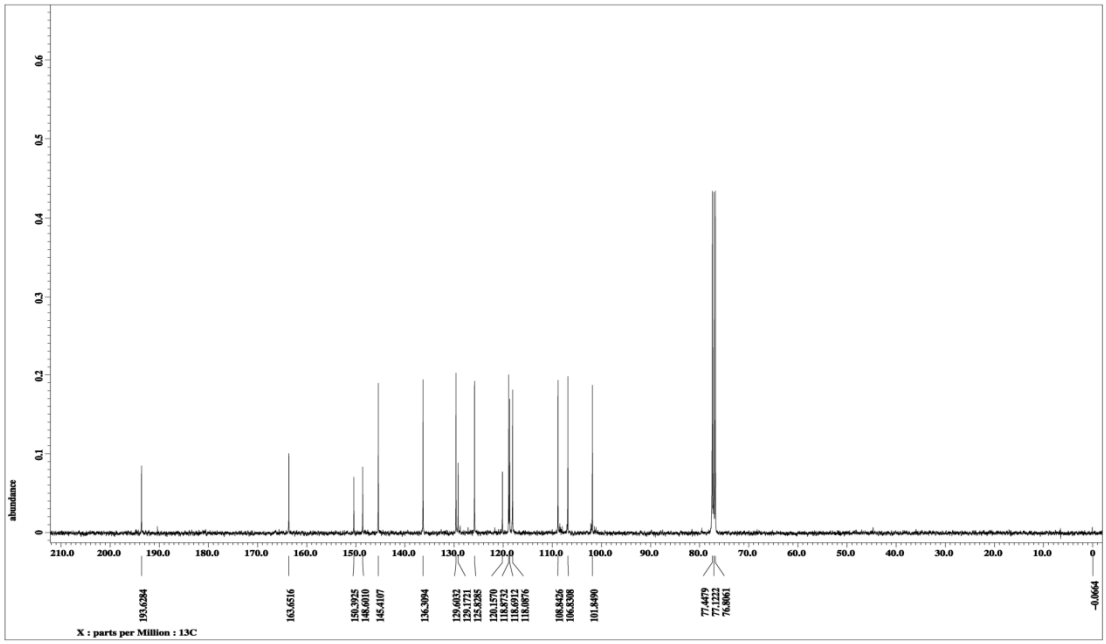




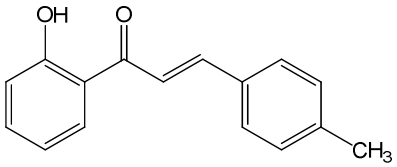
^{1}HNMR and ^{13}CNMR of (*E*)-3-(benzo[d][1,3]dioxol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one MC12

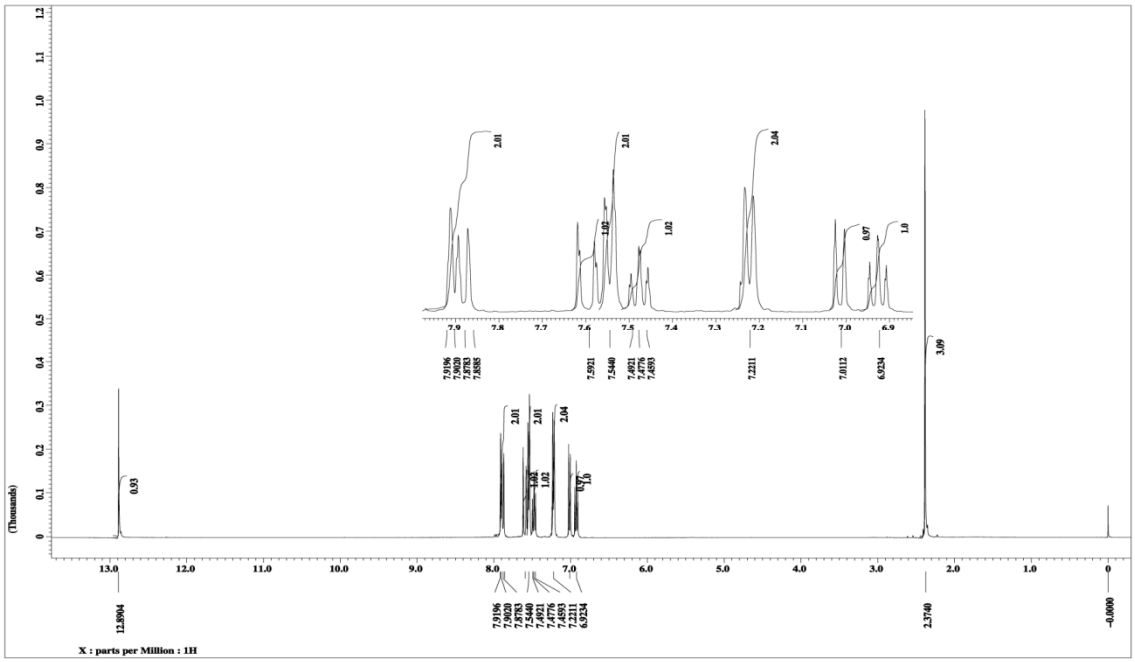


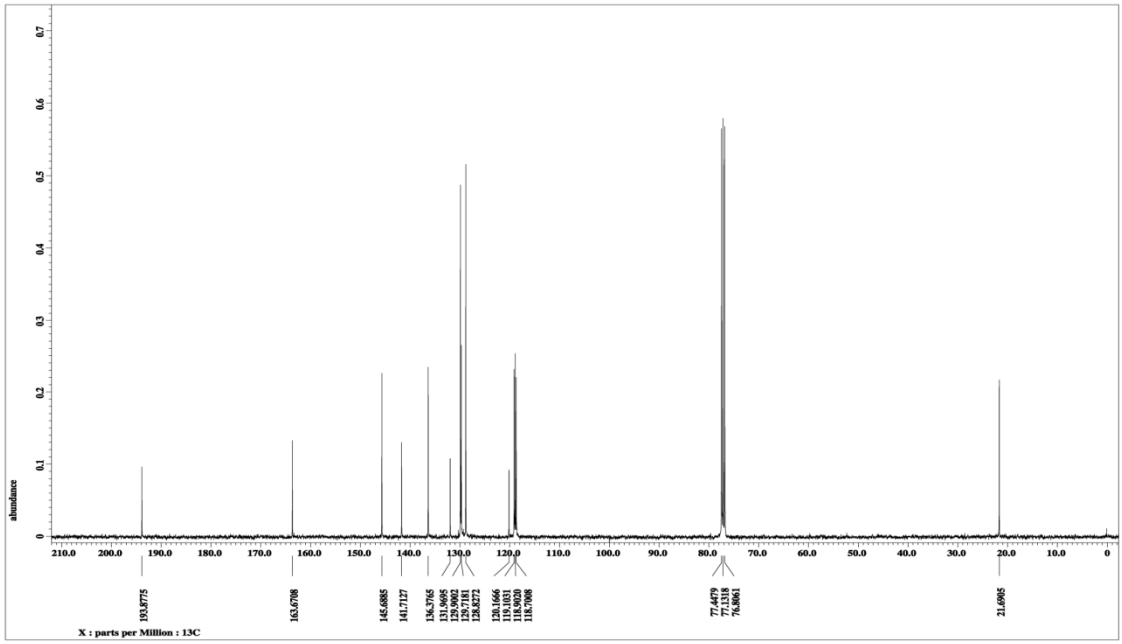




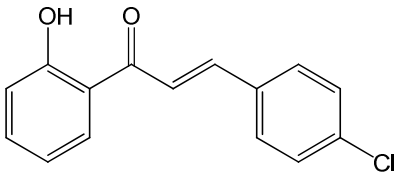
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-hydroxyphenyl)-3-p-tolylprop-2-en-1-one MC13

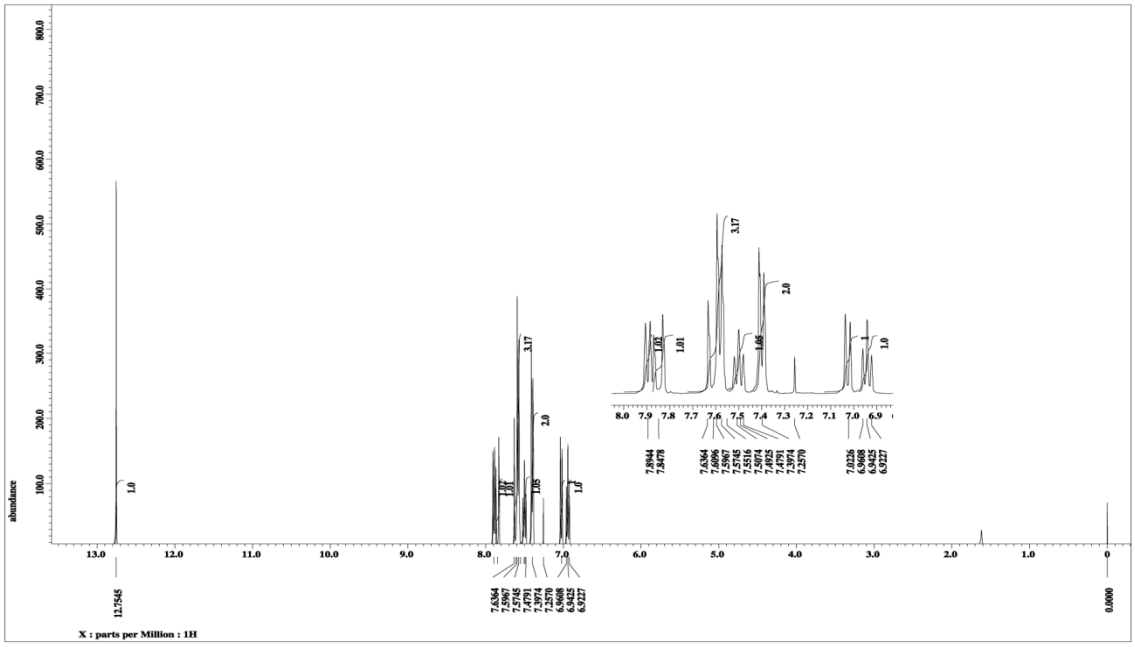


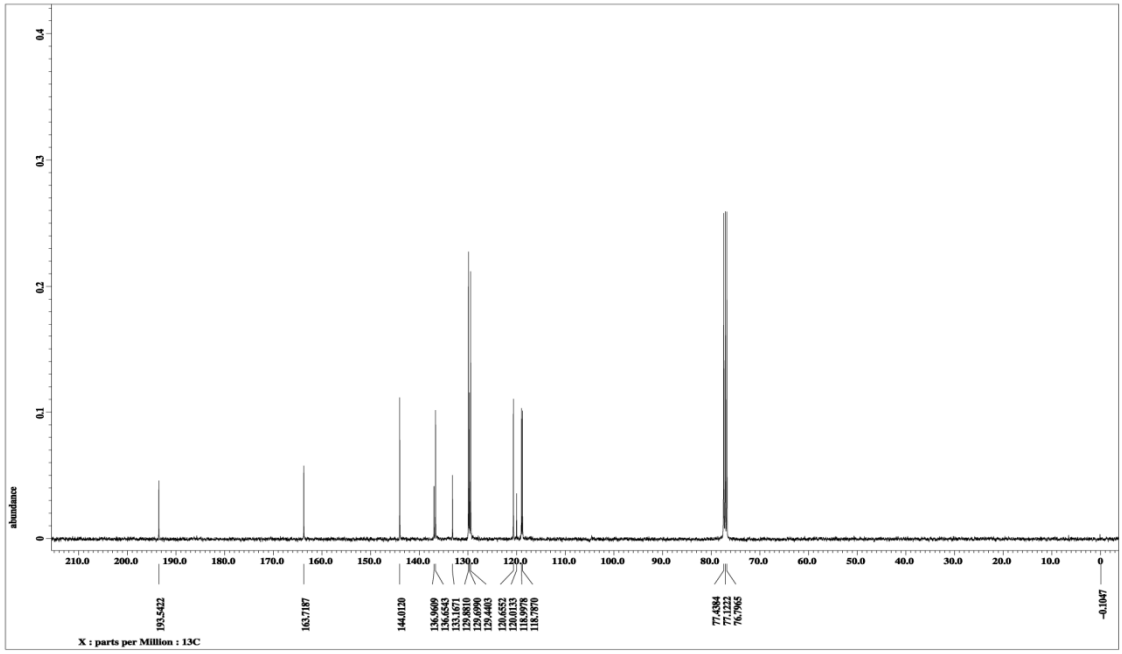




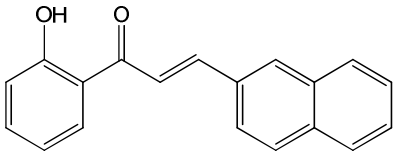
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-chlorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one MC14

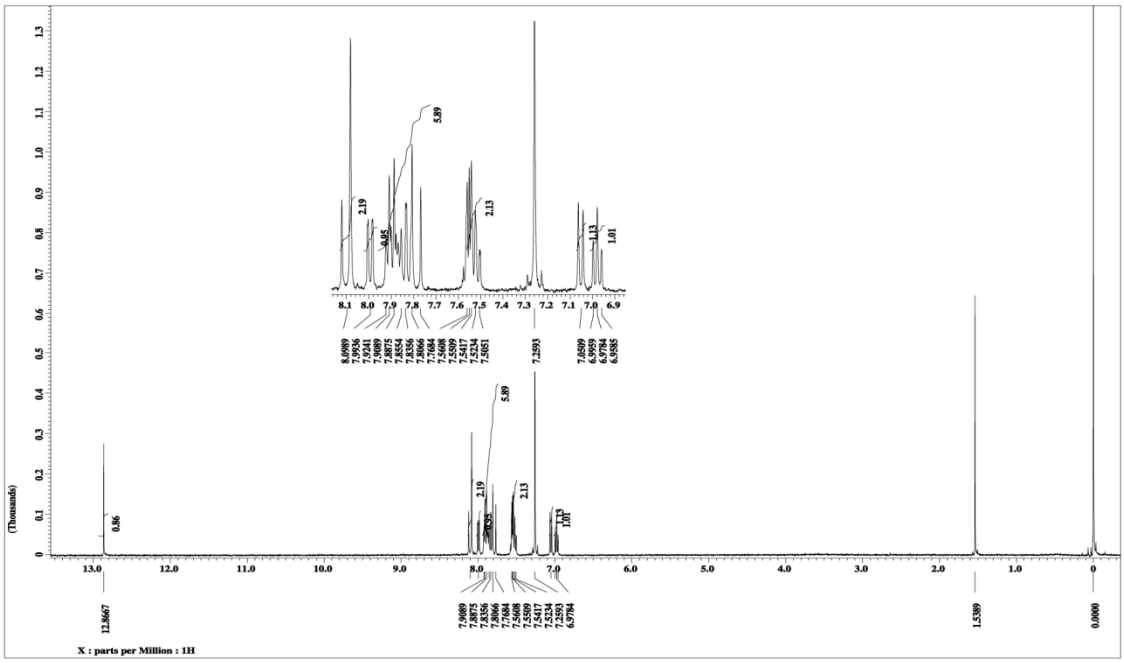


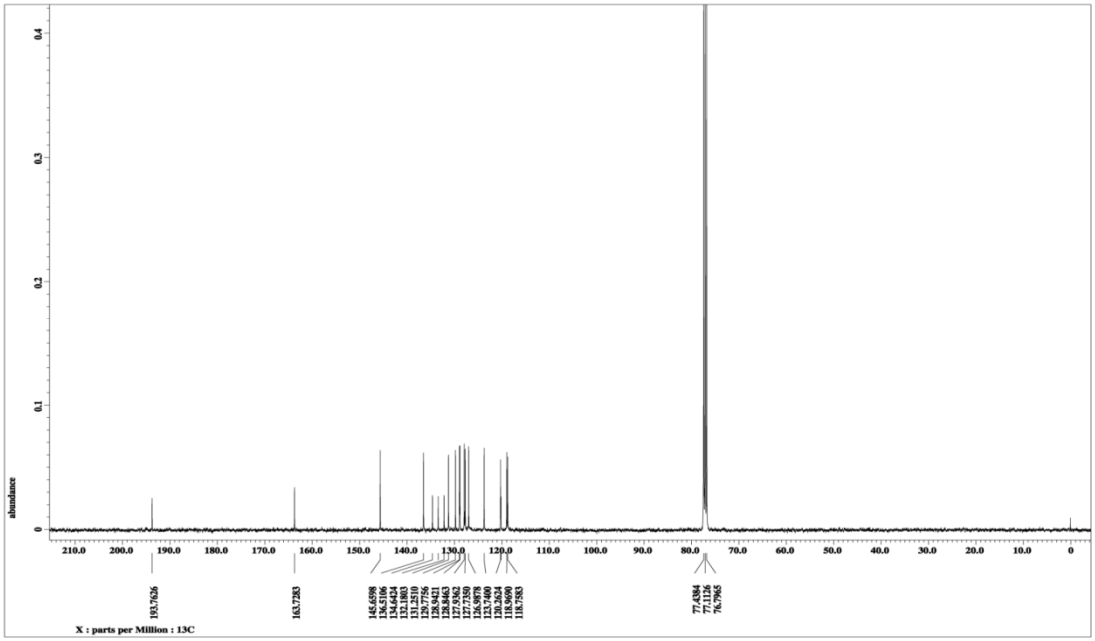




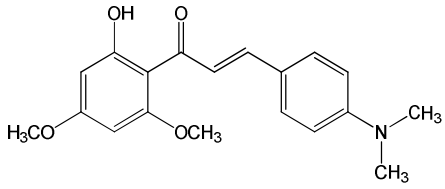
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-hydroxyphenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC15

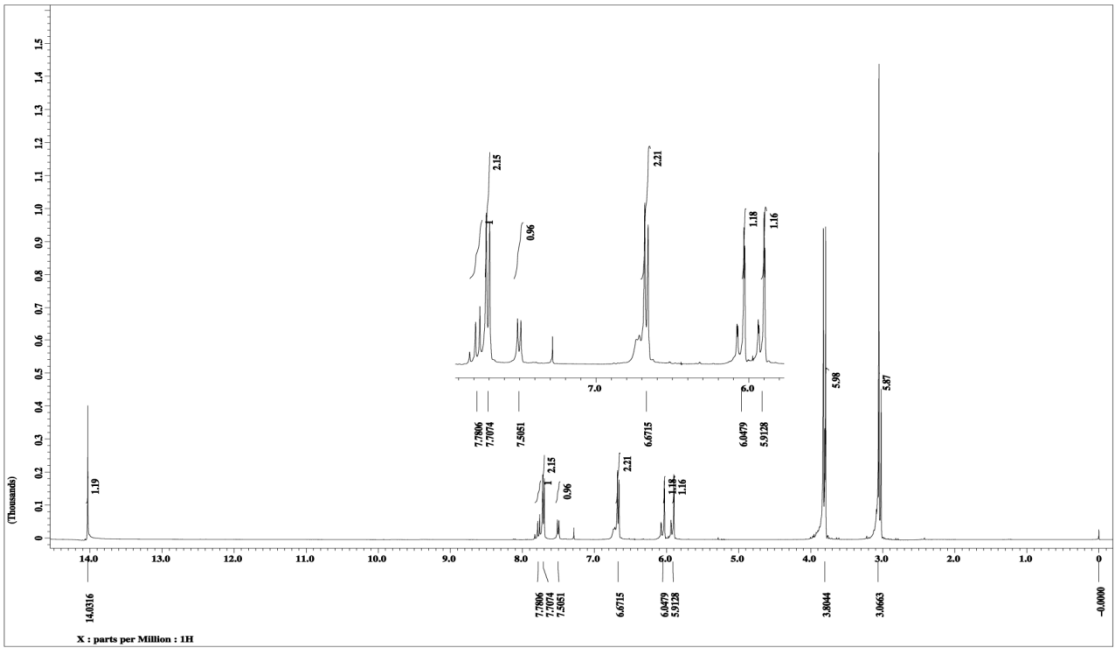


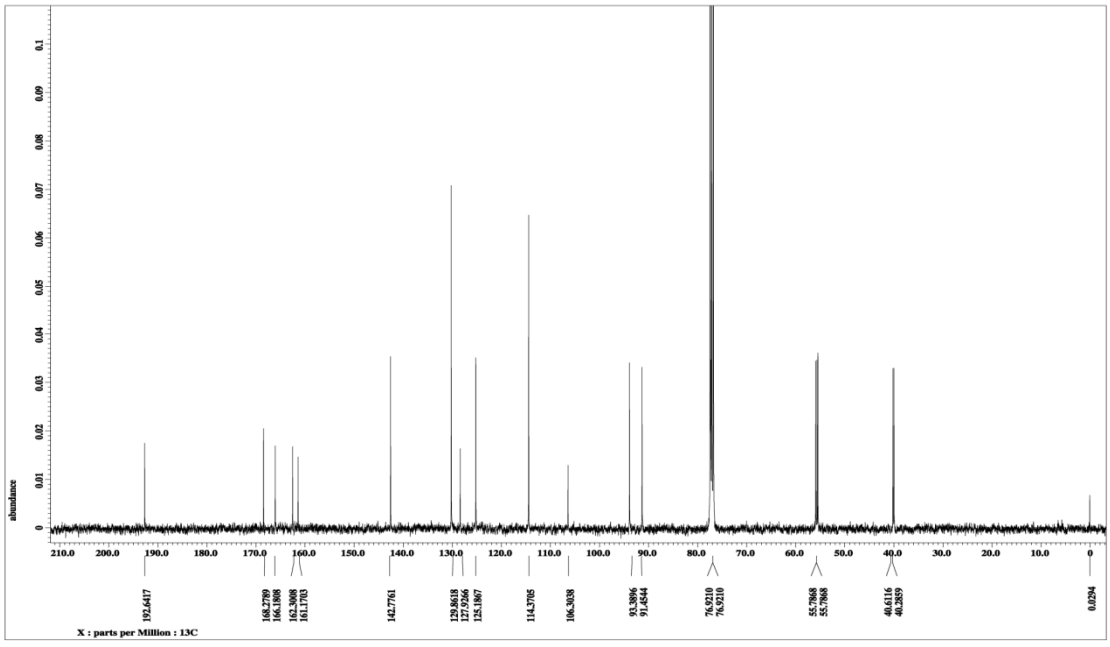




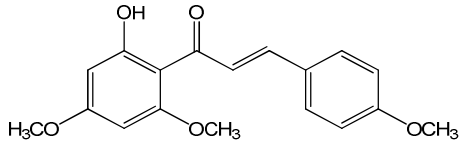
[1]HNMR and [13]CNMR of (*E*)-3-(4-(dimethylamino) phenyl)-1-(2-hydroxy-4, 6-dimethoxyphenyl) prop-2-en-1-one MC16

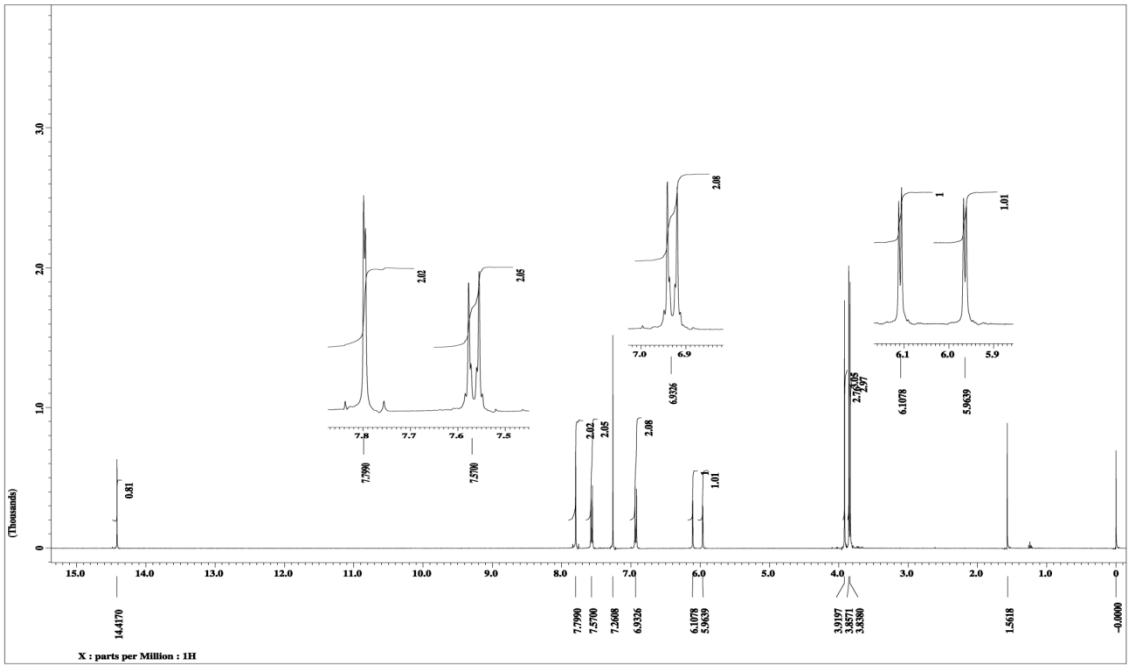


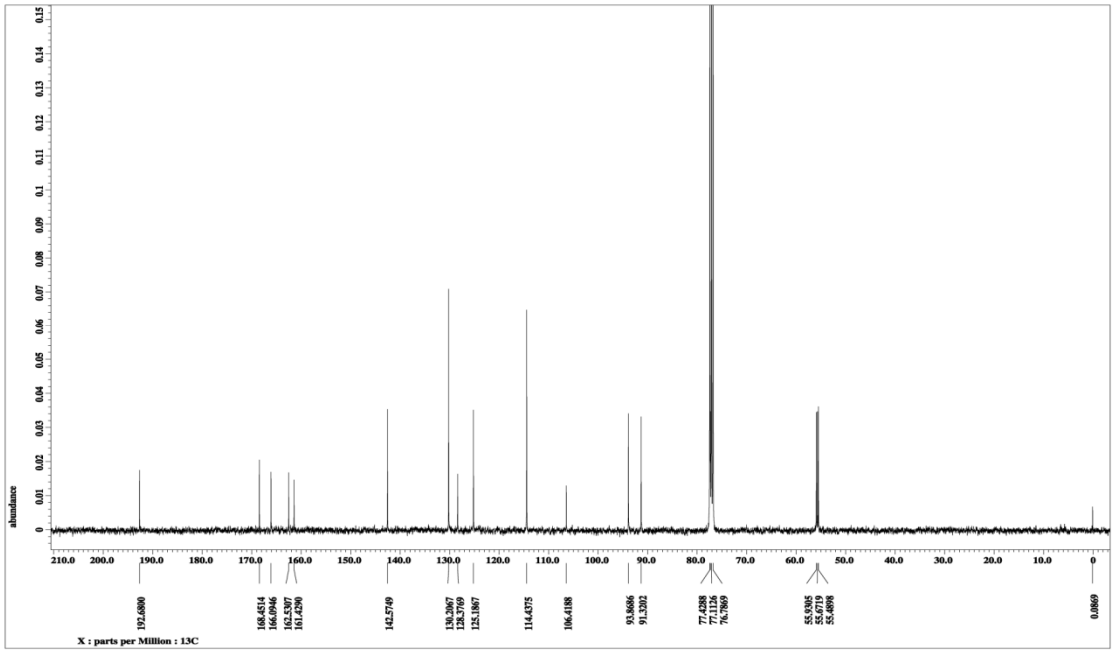




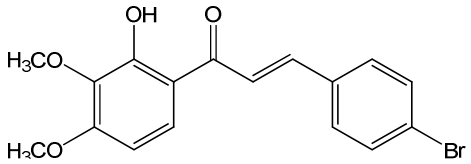
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-hydroxy-4, 6-dimethoxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one MC17

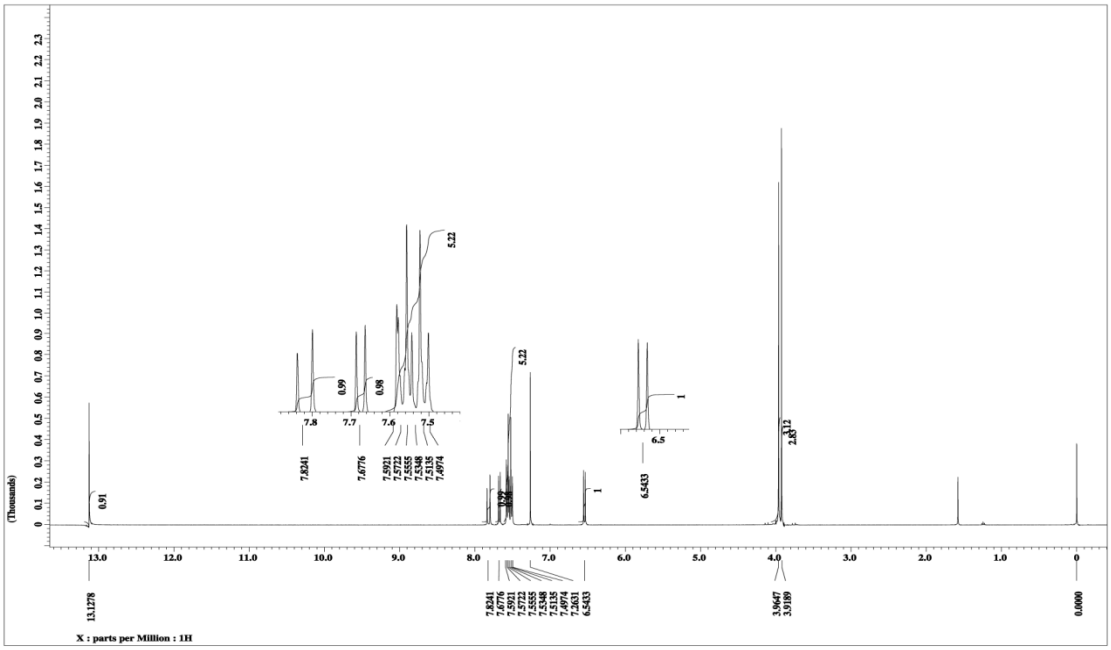


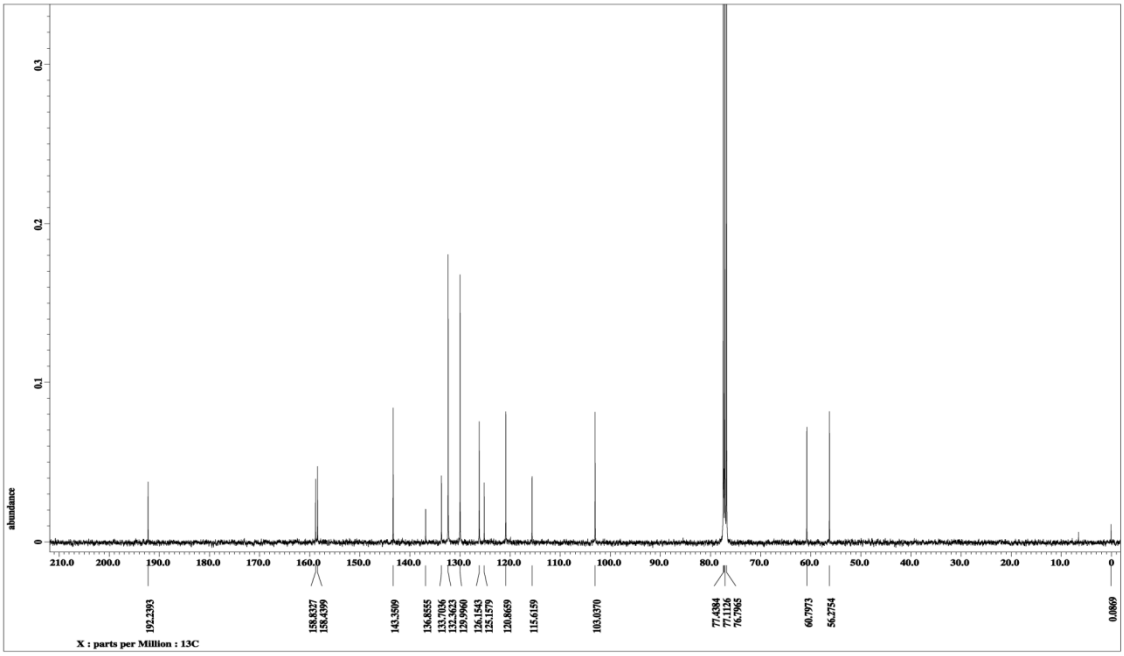




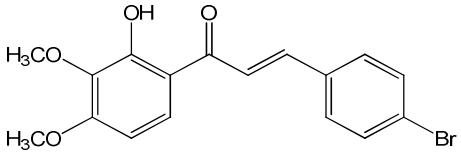
[1]HNMR and [13]CNMR of (*E*)-3-(4-bromophenyl)-1-(2-hydroxy-3, 4-dimethoxyphenyl) prop-2-en-1-one MC18

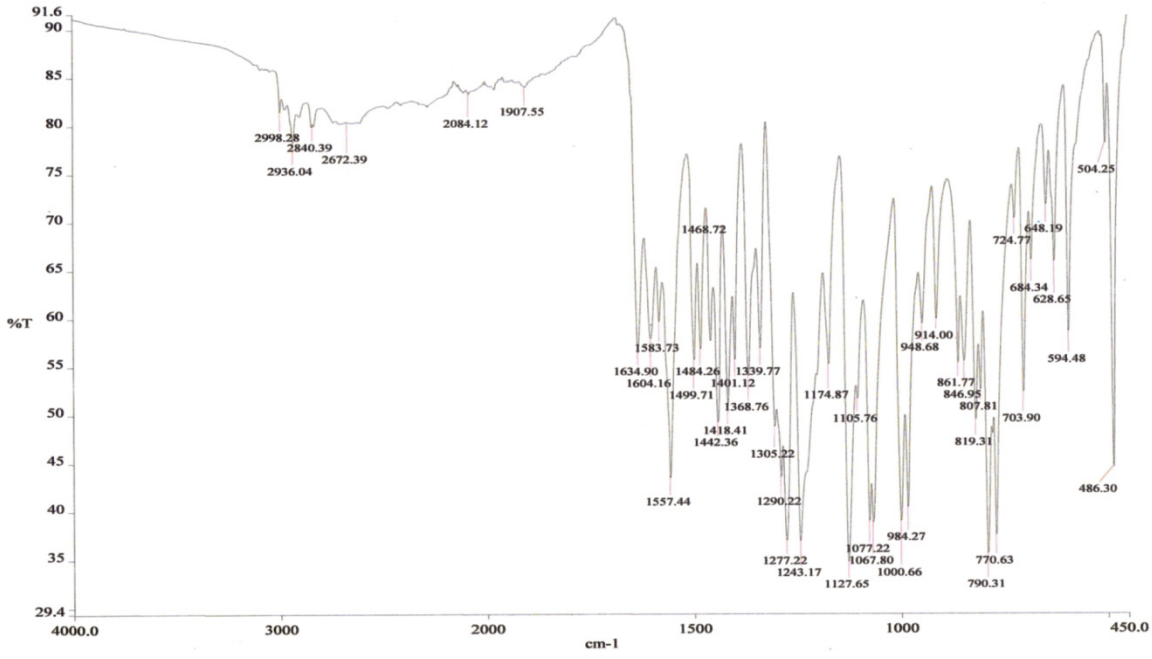




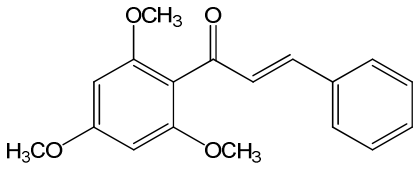


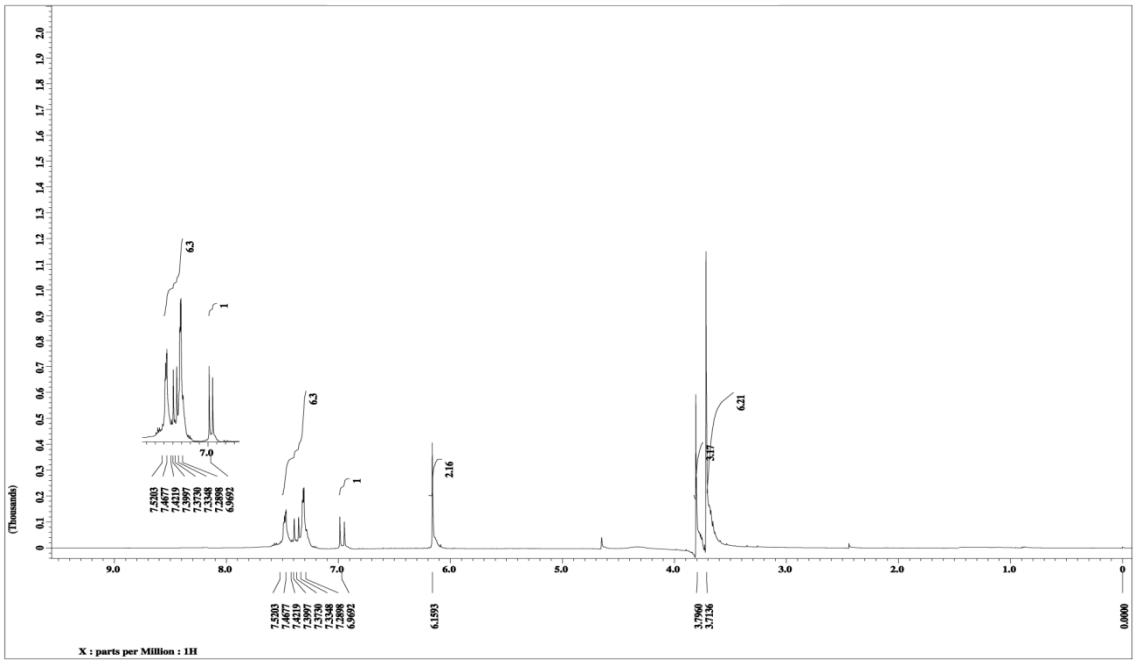
IR of (*E*)-3-(4-bromophenyl)-1-(2-hydroxy-3, 4-dimethoxyphenyl) prop-2-en-1-one MC18

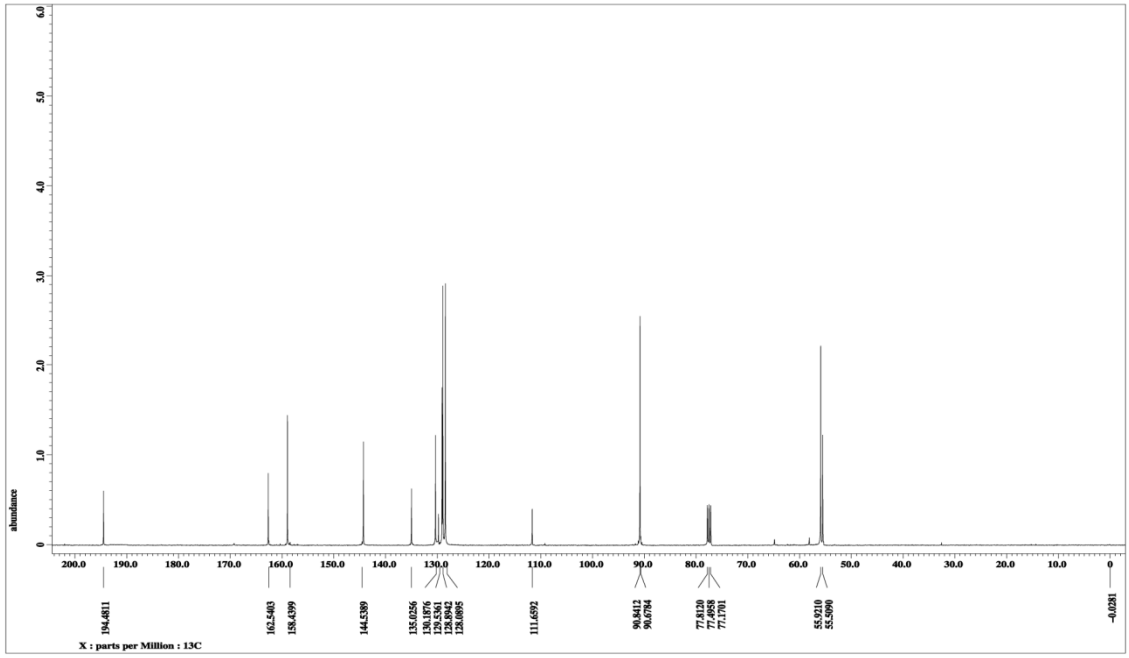




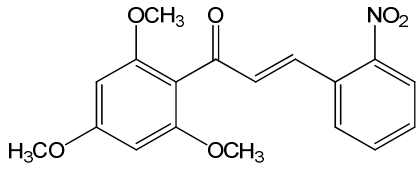
^{1}HNMR and ^{13}CNMR of (*E*)-3-phenyl-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one MC19

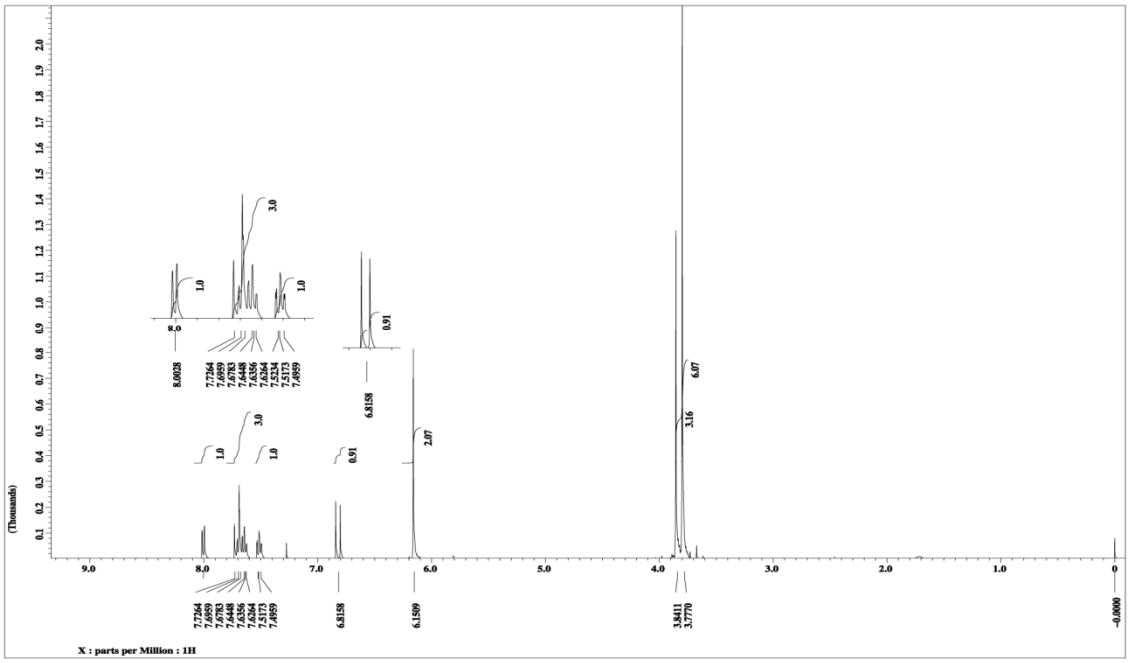


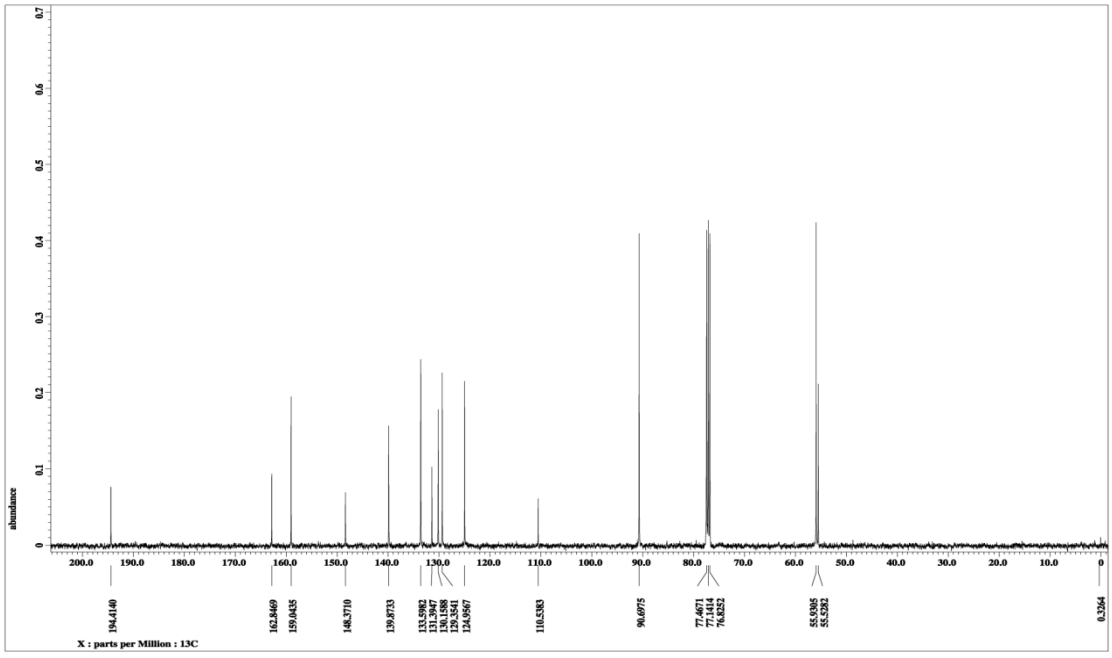




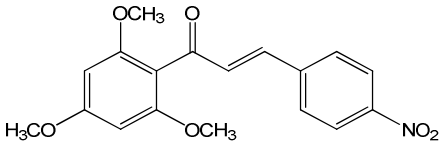
[1]HNMR and [13]CNMR of (*E*)-3-(2-nitrophenyl)-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one MC20

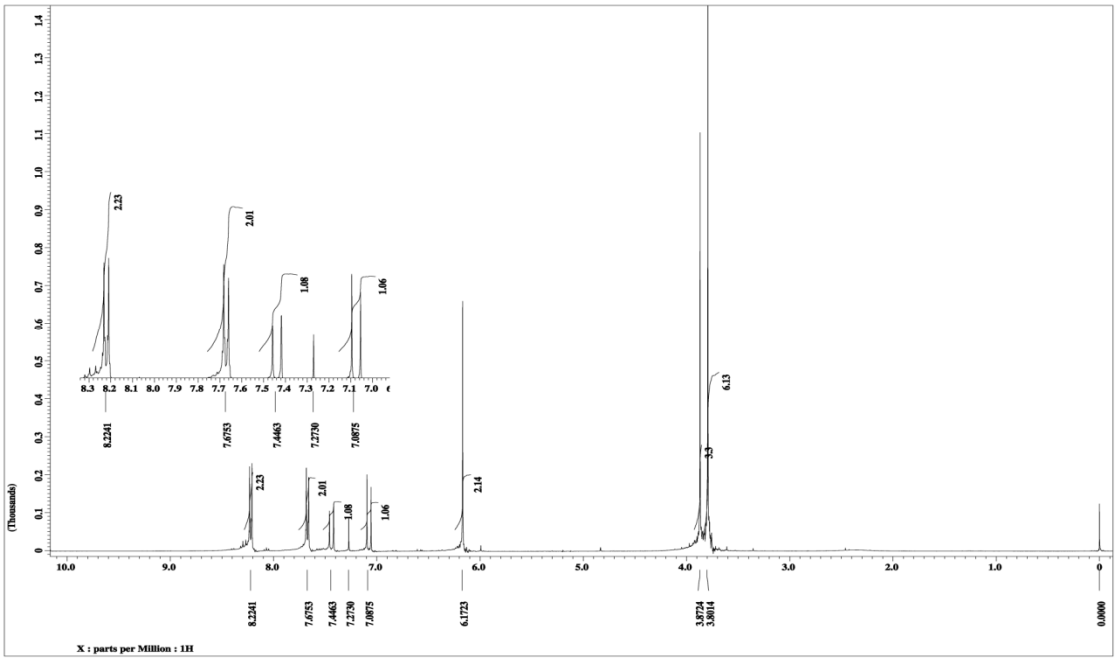


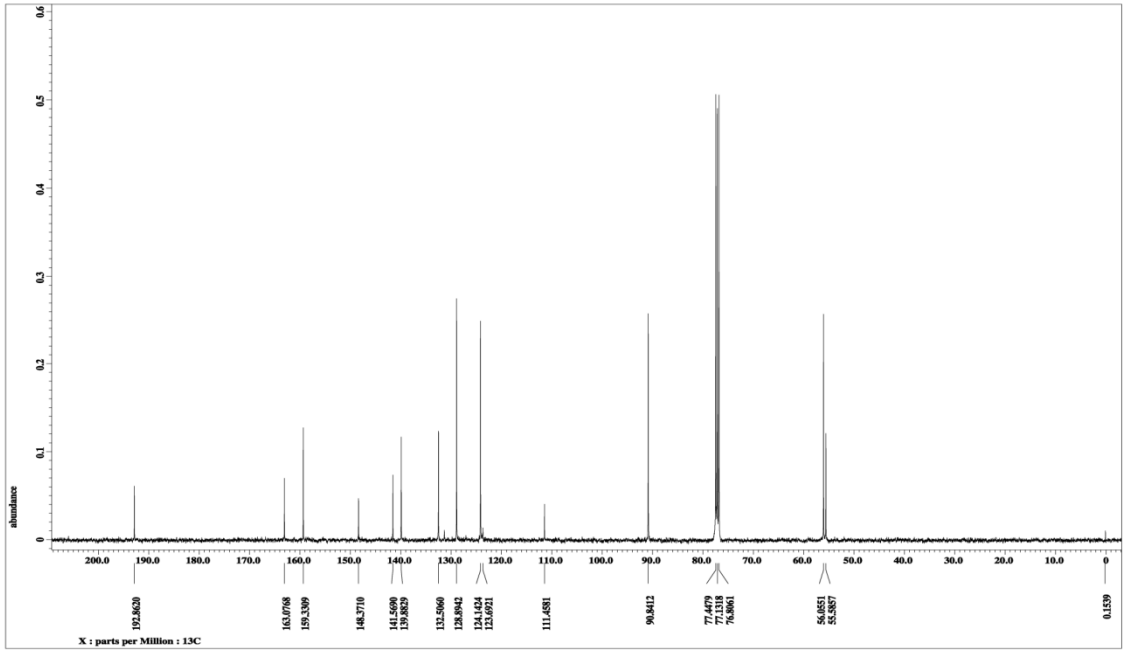




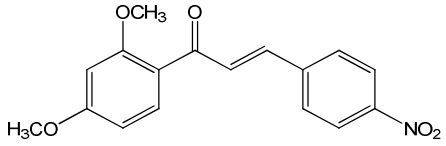
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-nitrophenyl)-1-(2, 4, 6-trimethoxyphenyl) prop-2-en-1-one MC21

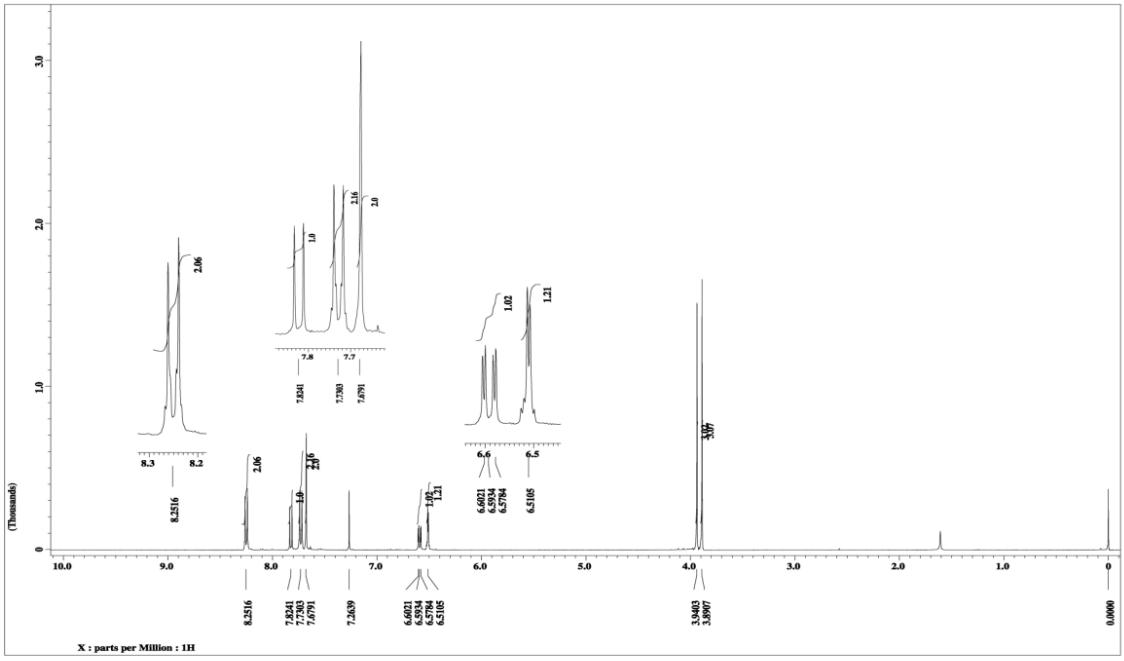


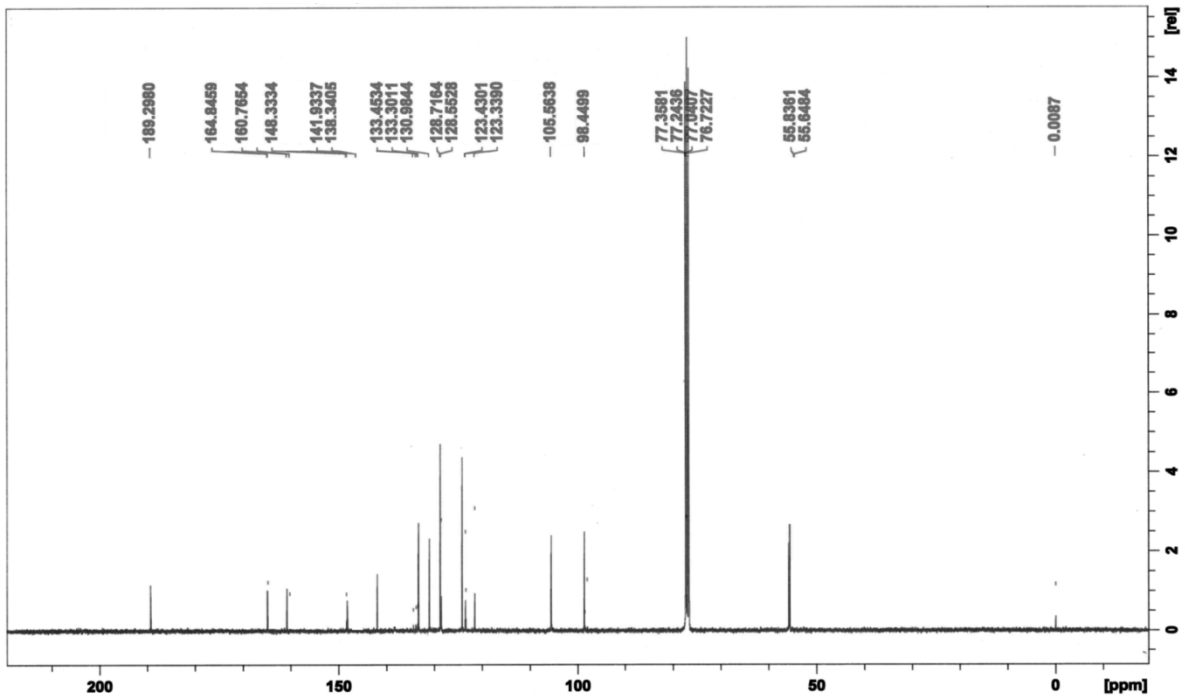




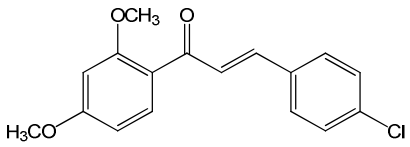
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2, 4-dimethoxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one MC22

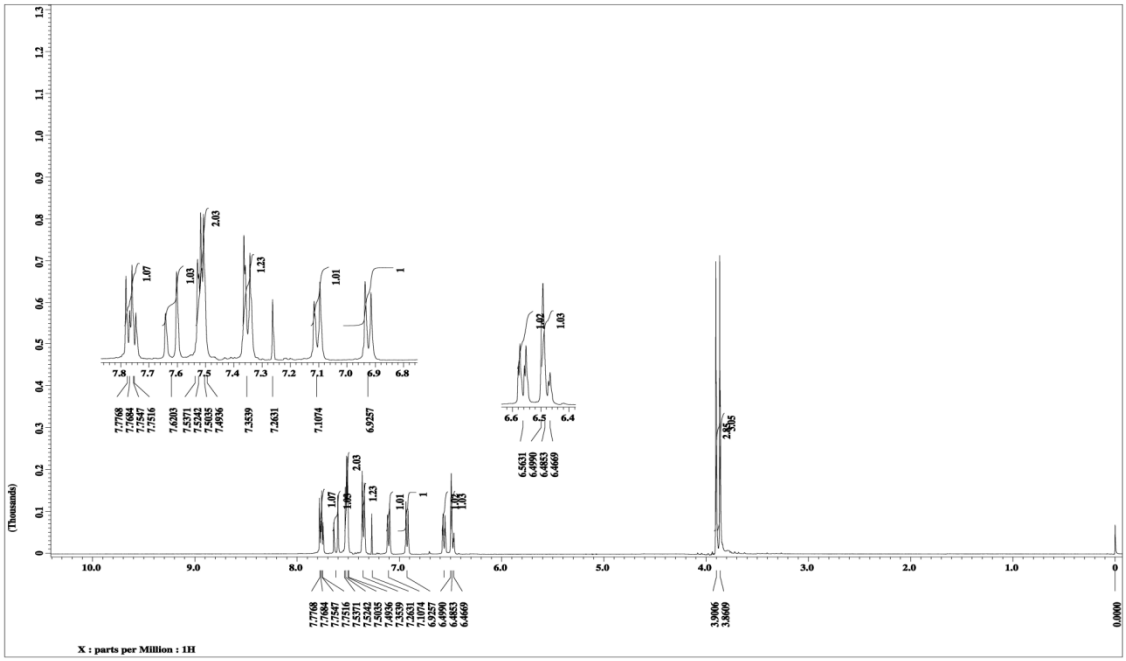


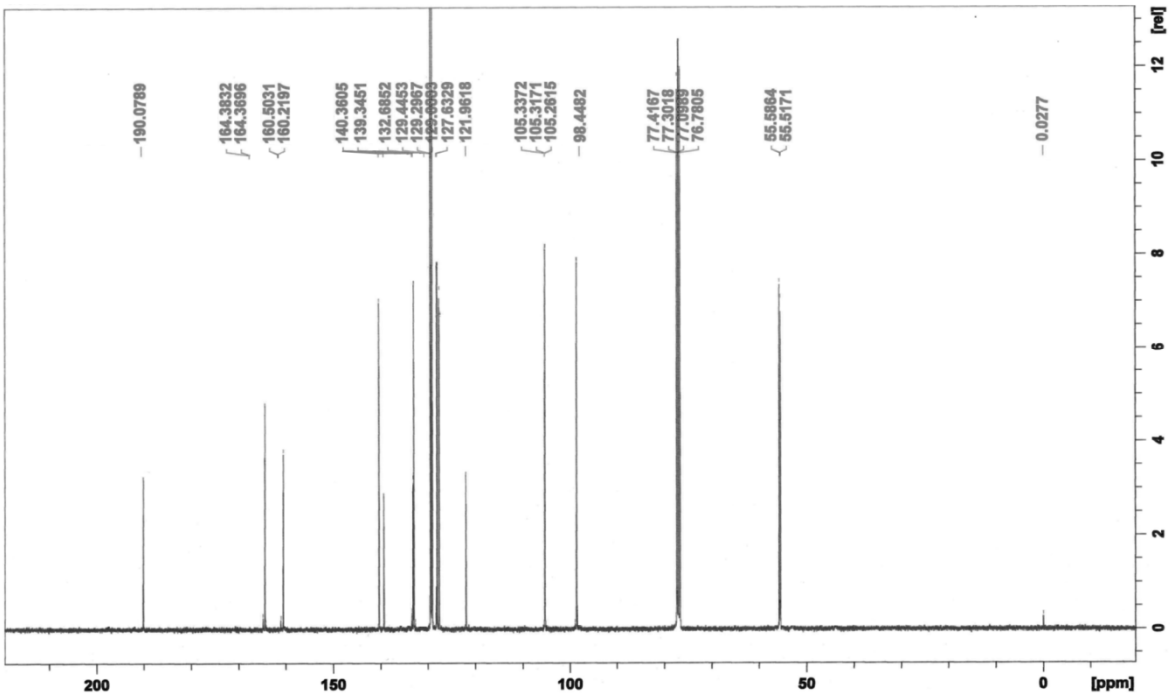




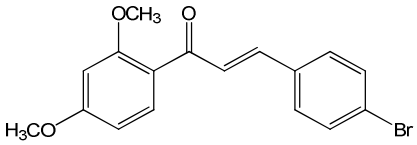
[1]HNMR and [13]CNMR of (*E*)-3-(4-chlorophenyl)-1-(2, 4-dimethoxyphenyl) prop-2-en-1-one MC23

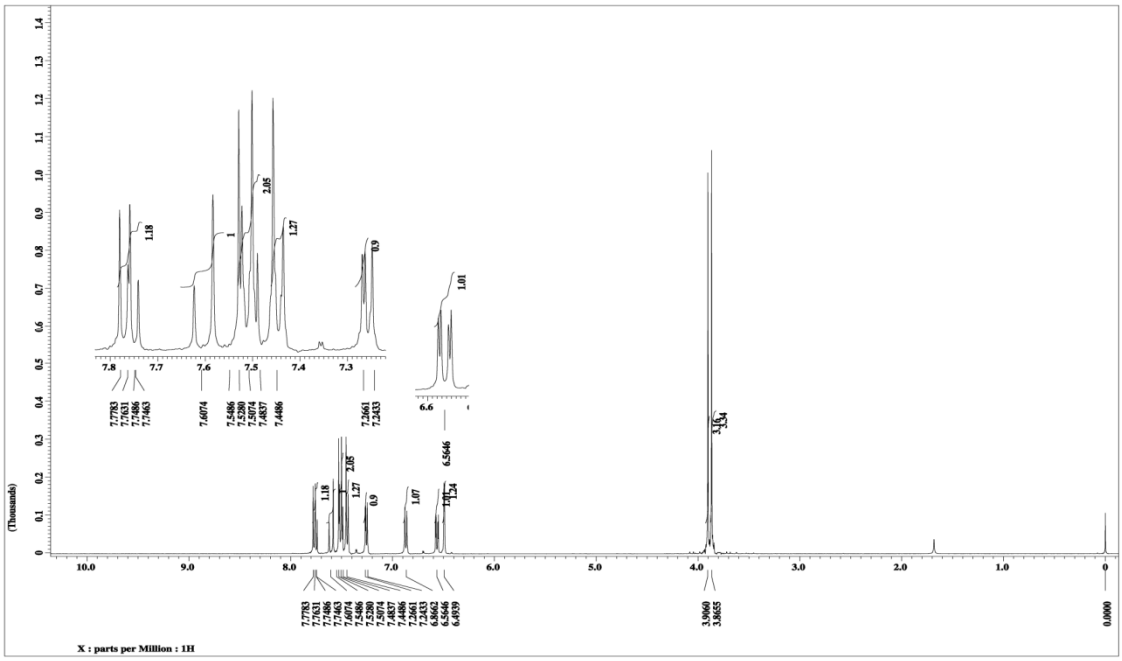


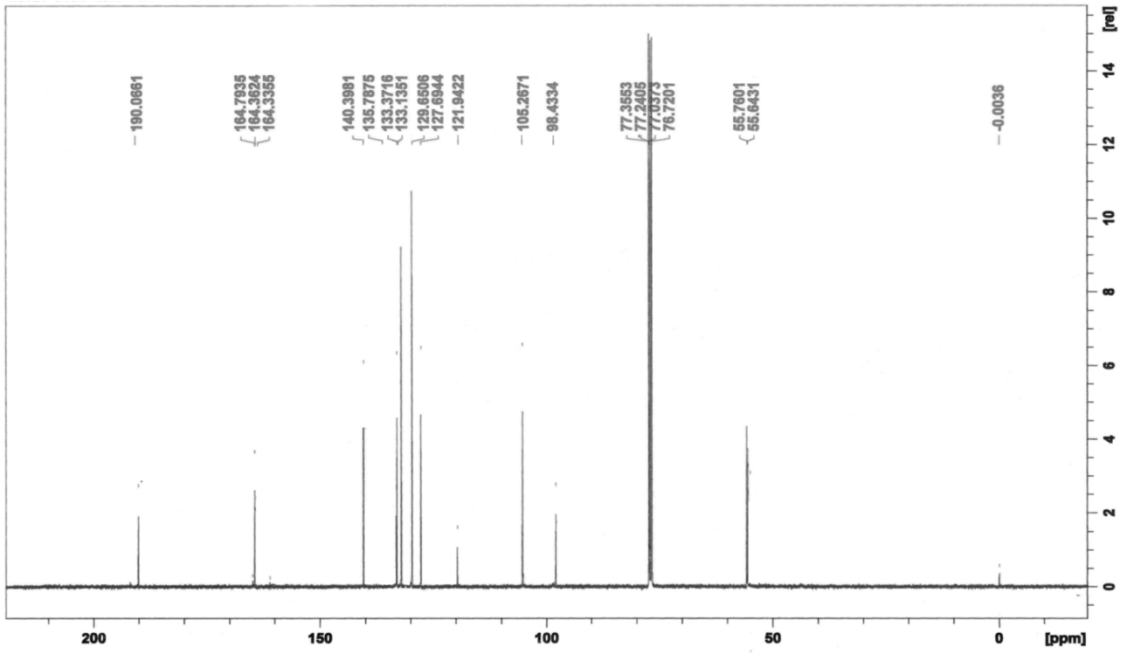




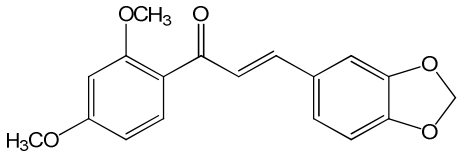
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-bromophenyl)-1-(2, 4-dimethoxyphenyl) prop-2-en-1-one MC24

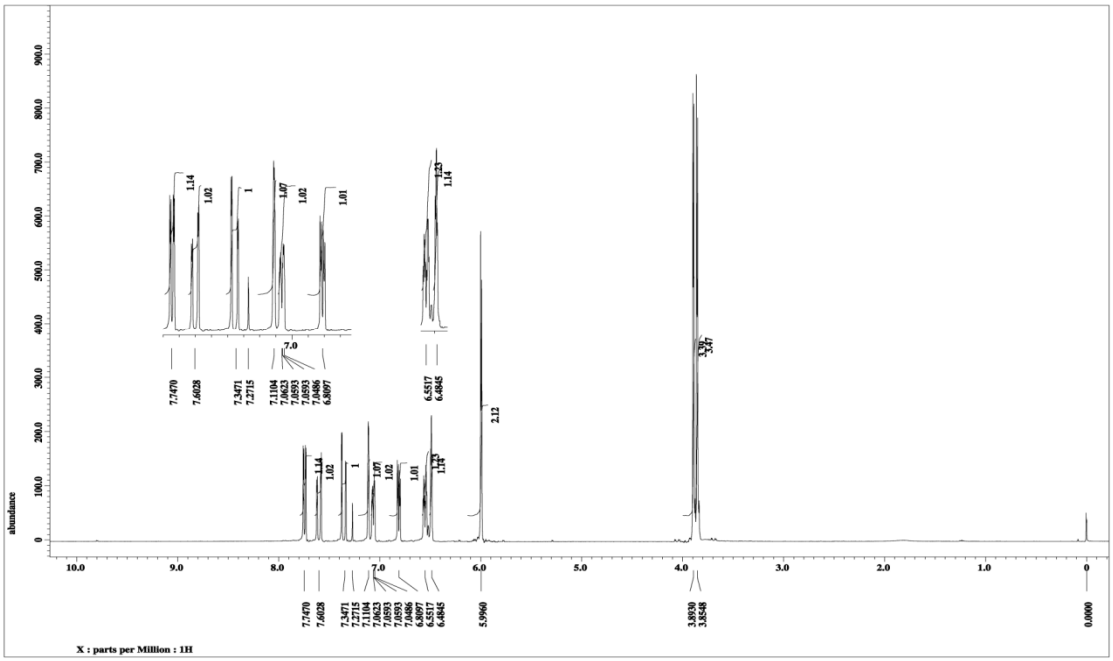


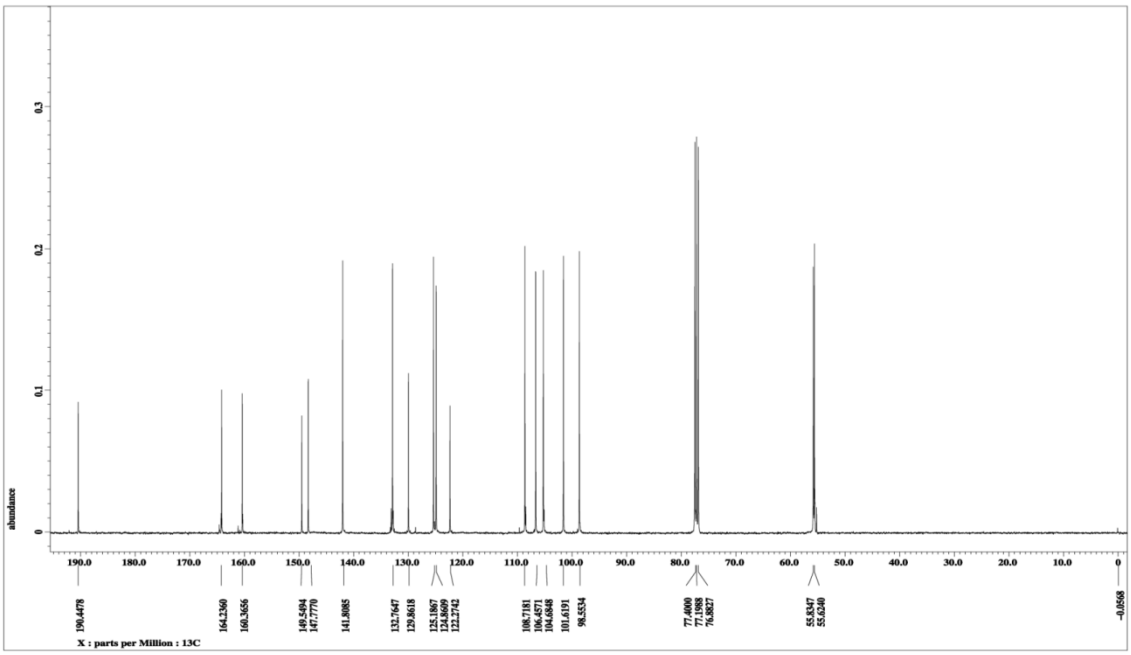




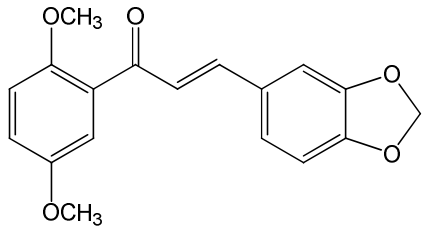
^{1}HNMR and ^{13}CNMR of (*E*)-3-(benzo[d] [1, 3] dioxol-5-yl)-1-(2, 4-dimethoxyphenyl) prop-2-en-1-one MC25

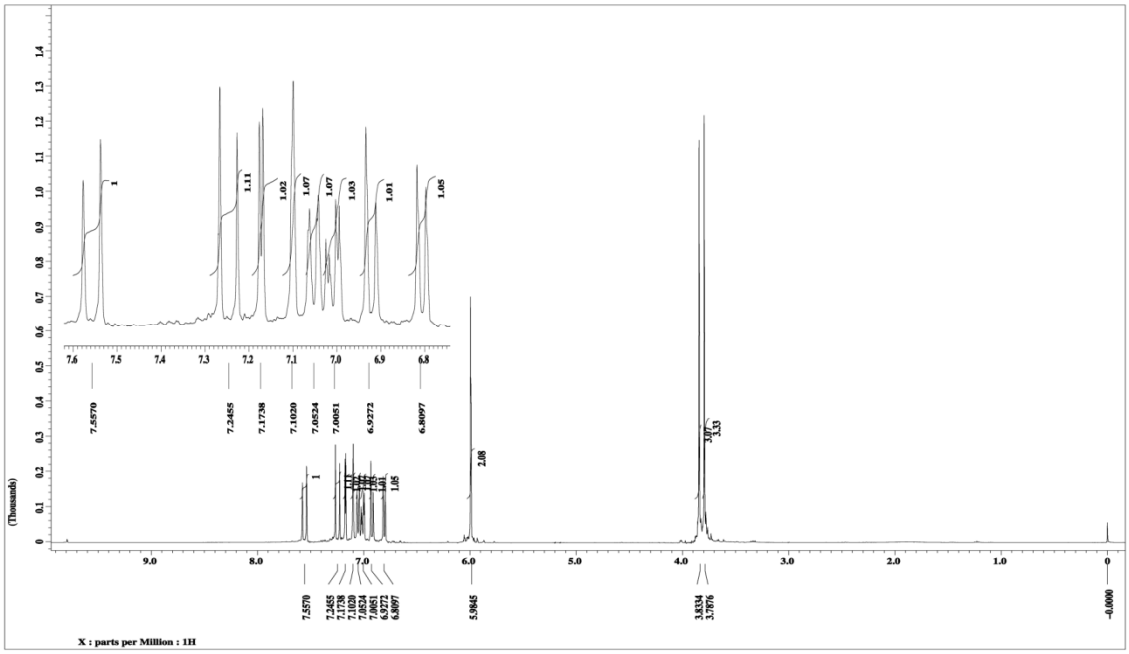


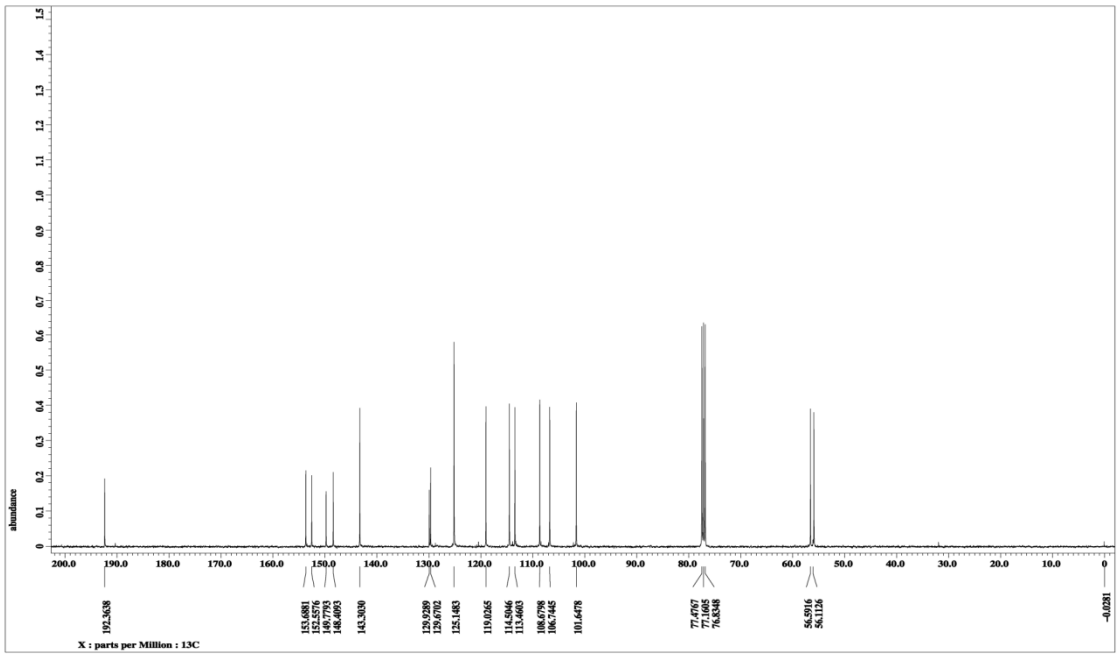




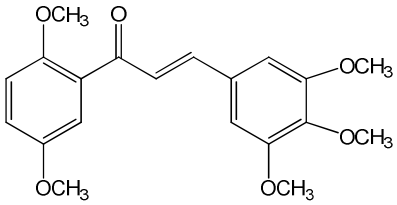
^{1}HNMR and ^{13}CNMR of (*E*)-3-(benzo[d] [1, 3] dioxol-5-yl)-1-(2, 5-dimethoxyphenyl) prop-2-en-1-one MC26

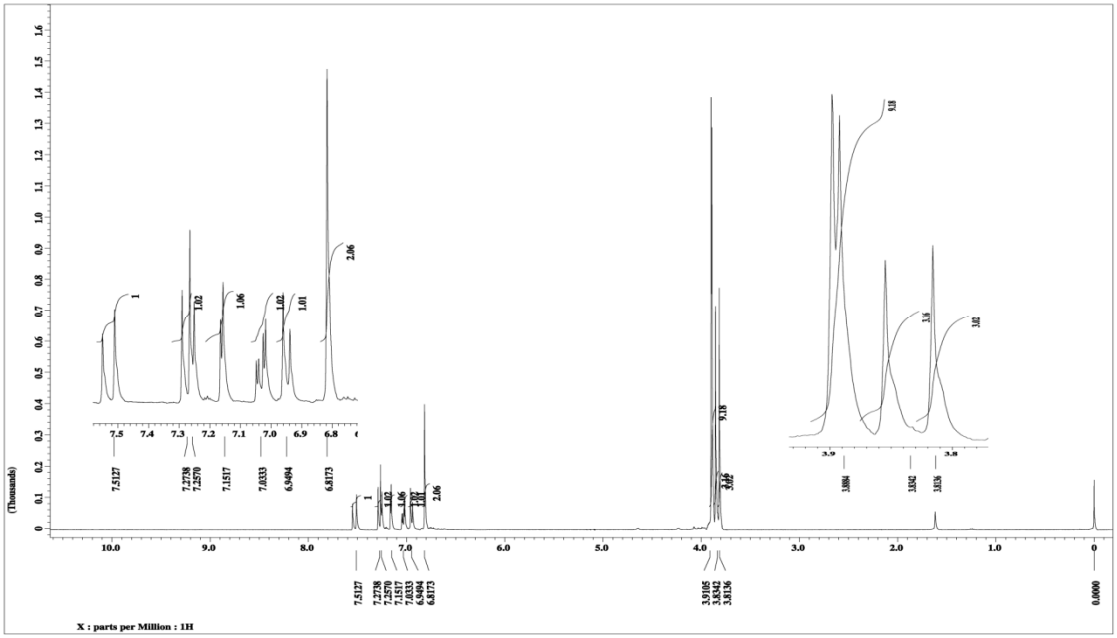


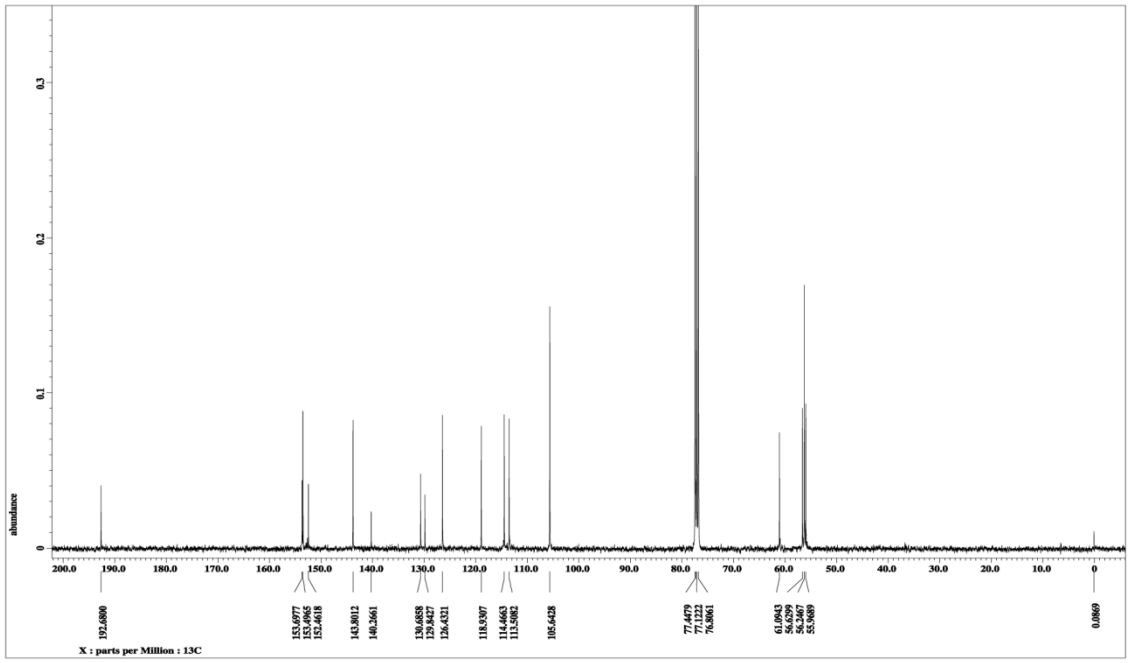




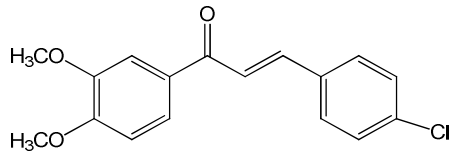
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2, 5-dimethoxyphenyl)-3-(3, 4, 5-trimethoxyphenyl) prop-2-en-1-one MC27

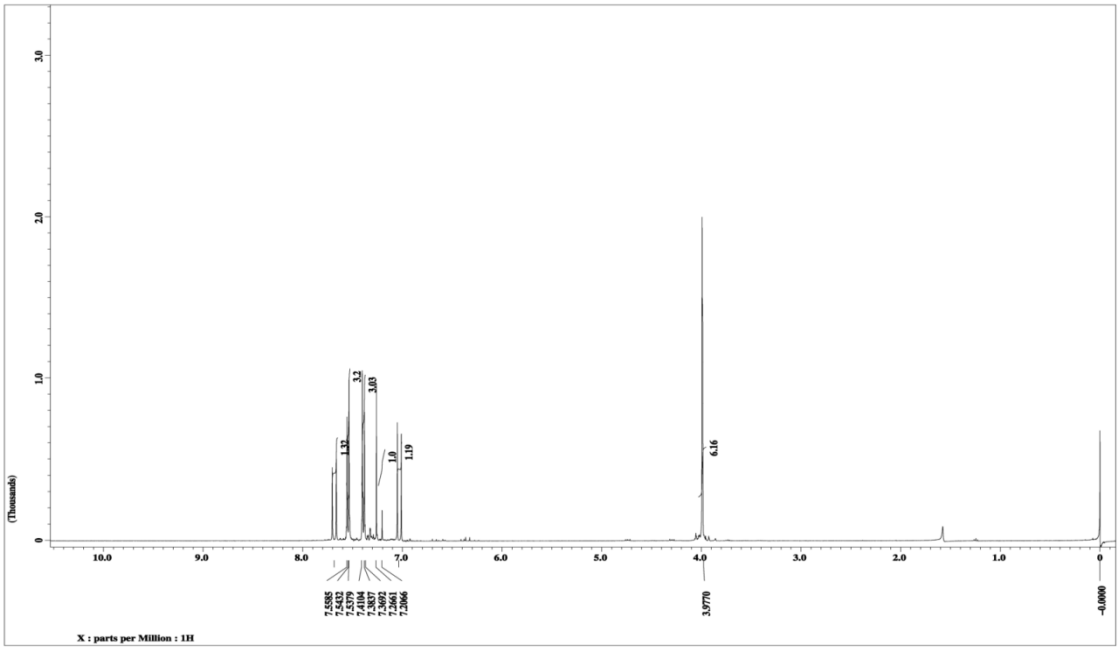


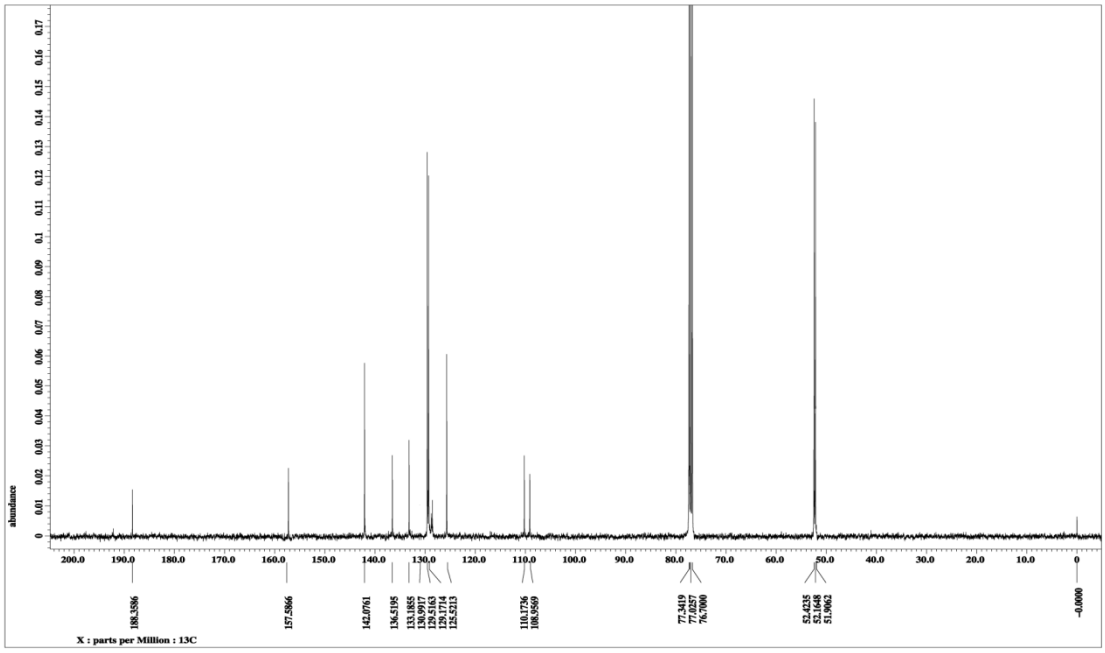




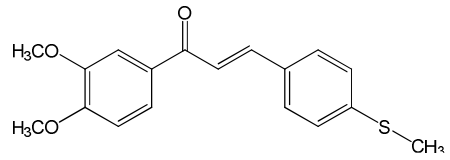
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-chlorophenyl)-1-(3, 4-dimethoxyphenyl) prop-2-en-1-one MC28

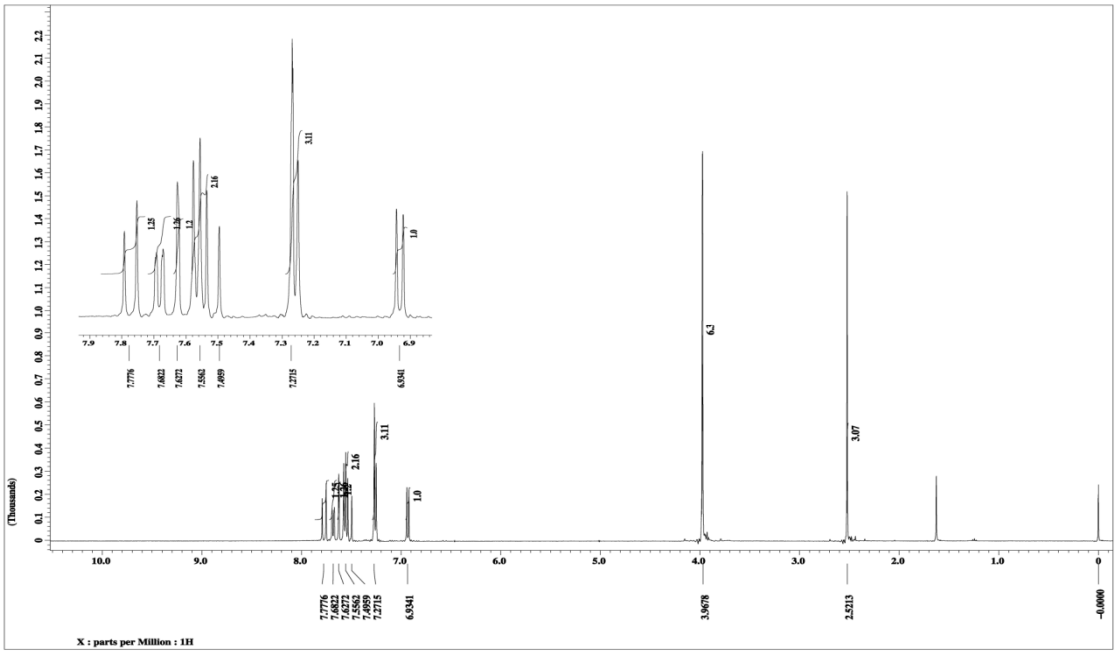


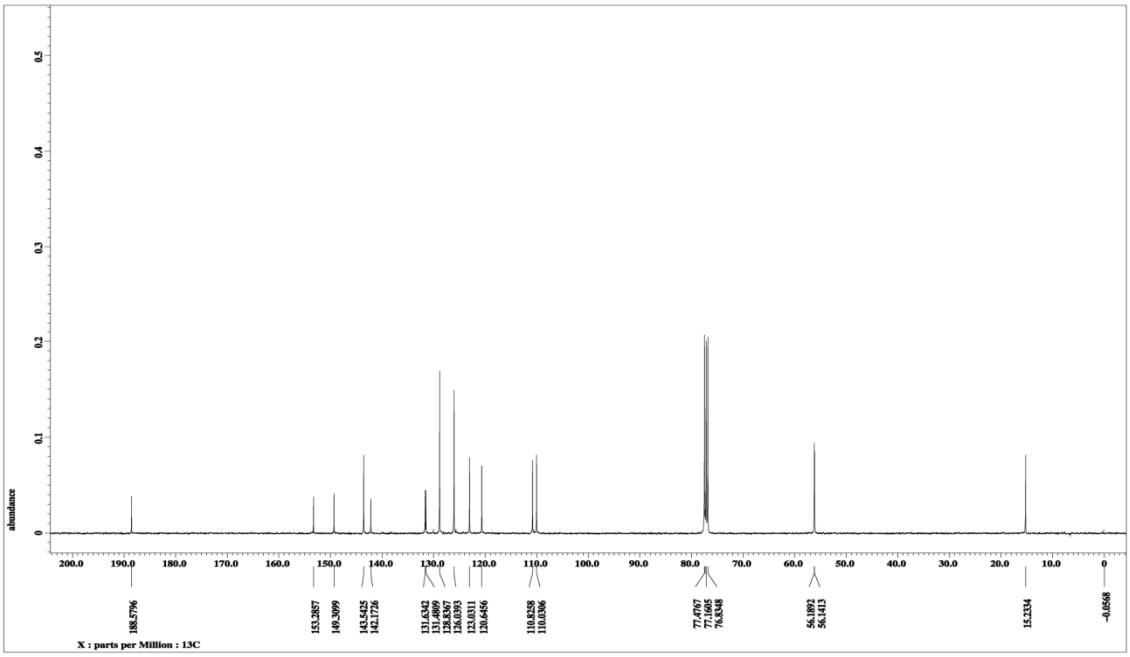




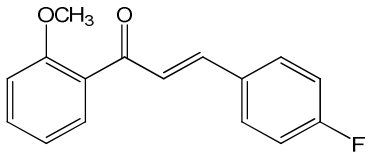
[1]HNMR and [13]CNMR of (*E*)-1-(3, 4-dimethoxyphenyl)-3-(4-(methylthio) phenyl) prop-2-en-1-one MC29

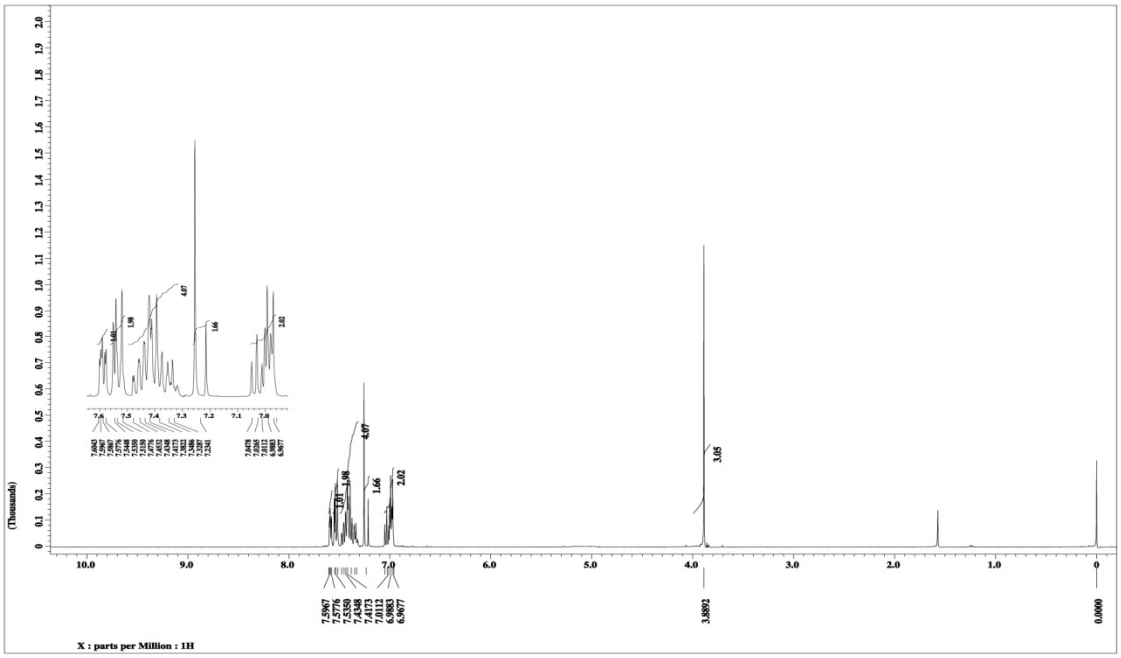


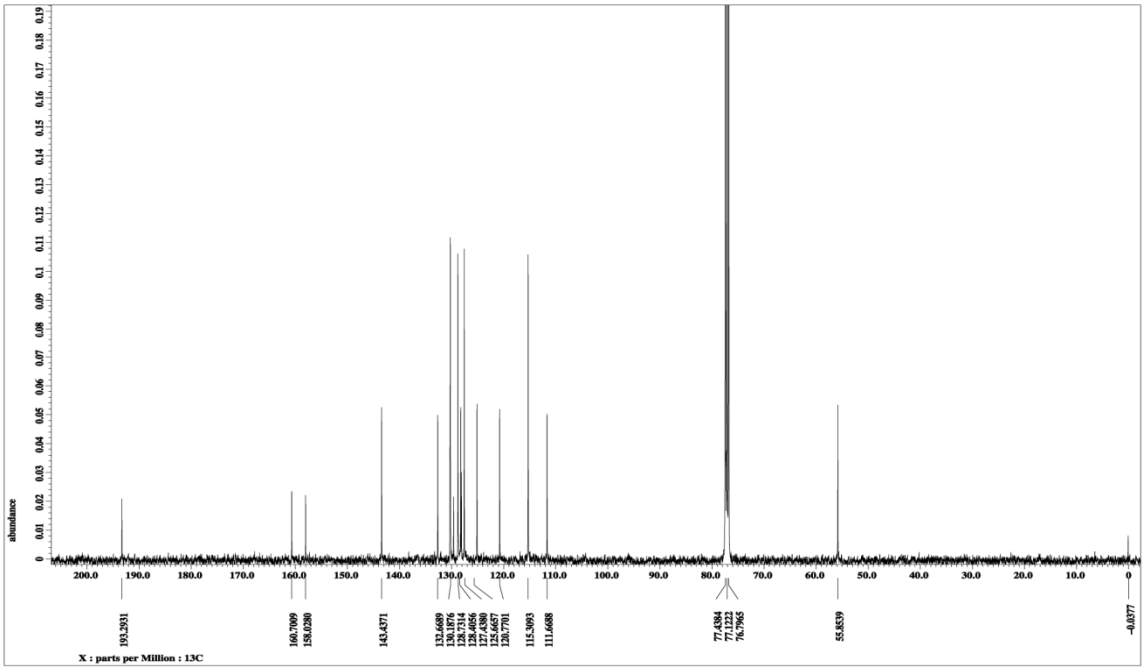




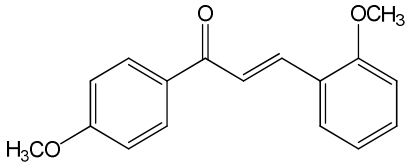
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-fluorophenyl)-1-(2-methoxyphenyl) prop-2-en-1-one MC30

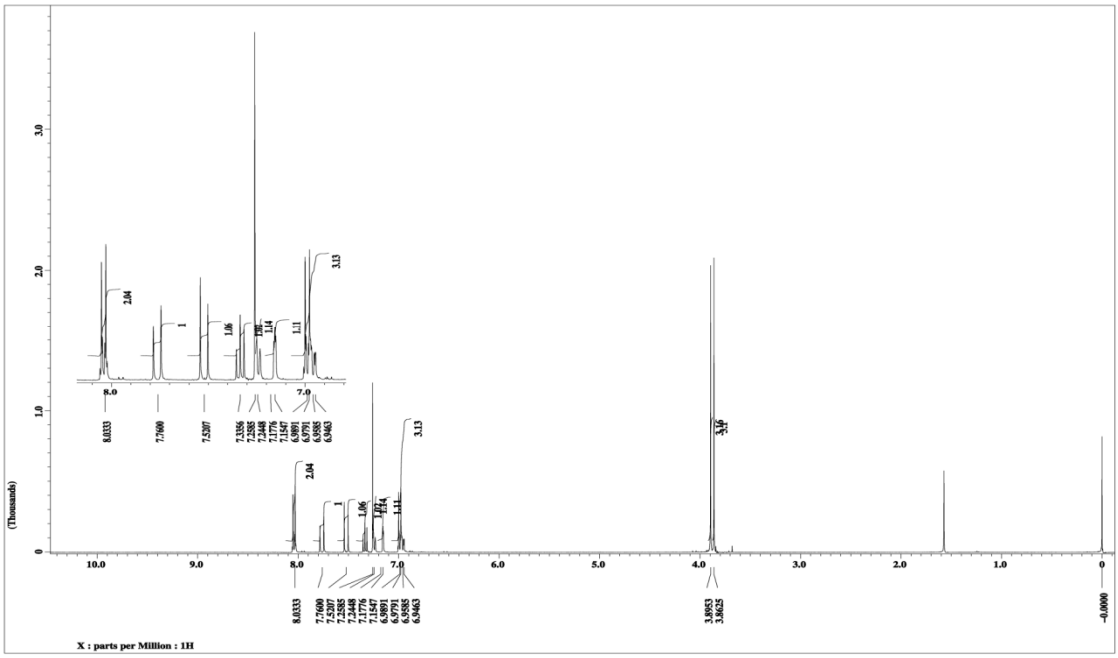


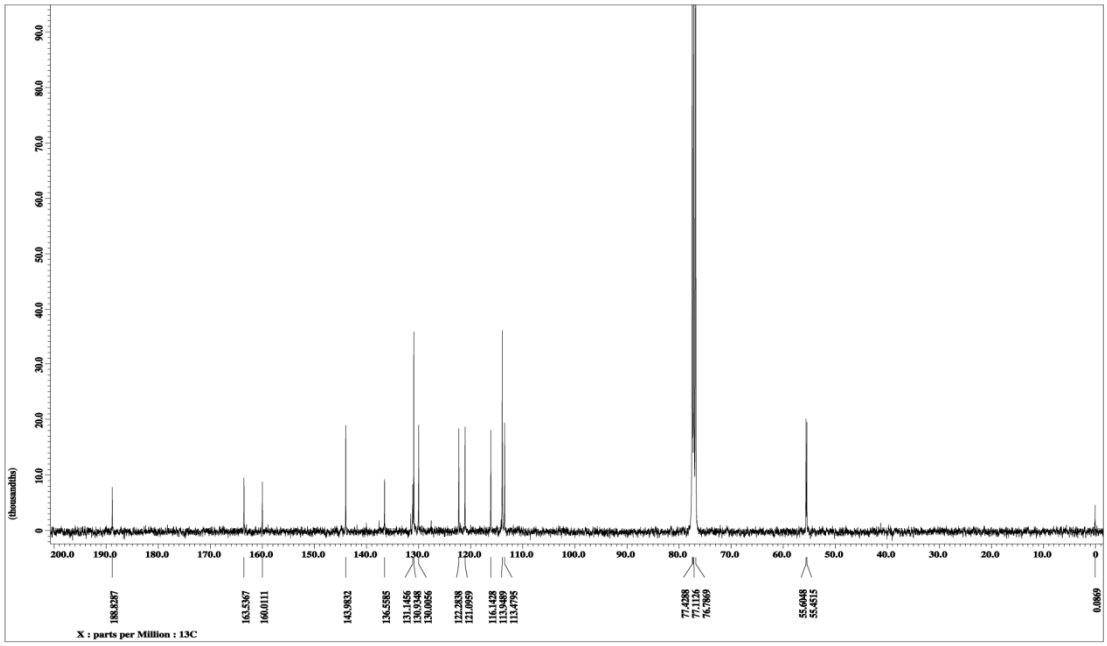




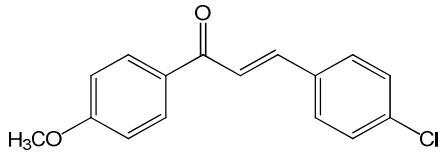
^{1}HNMR and ^{13}CNMR of (*E*)-3-(2-methoxyphenyl)-1-(4-methoxyphenyl) prop-2-en-1-one MC31

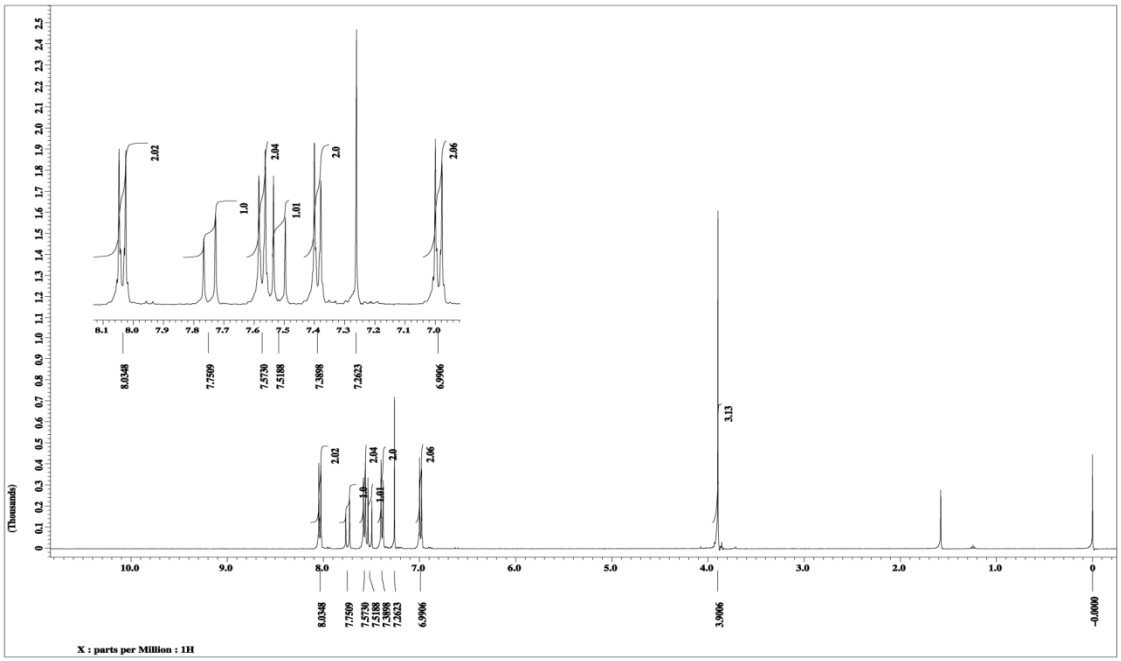


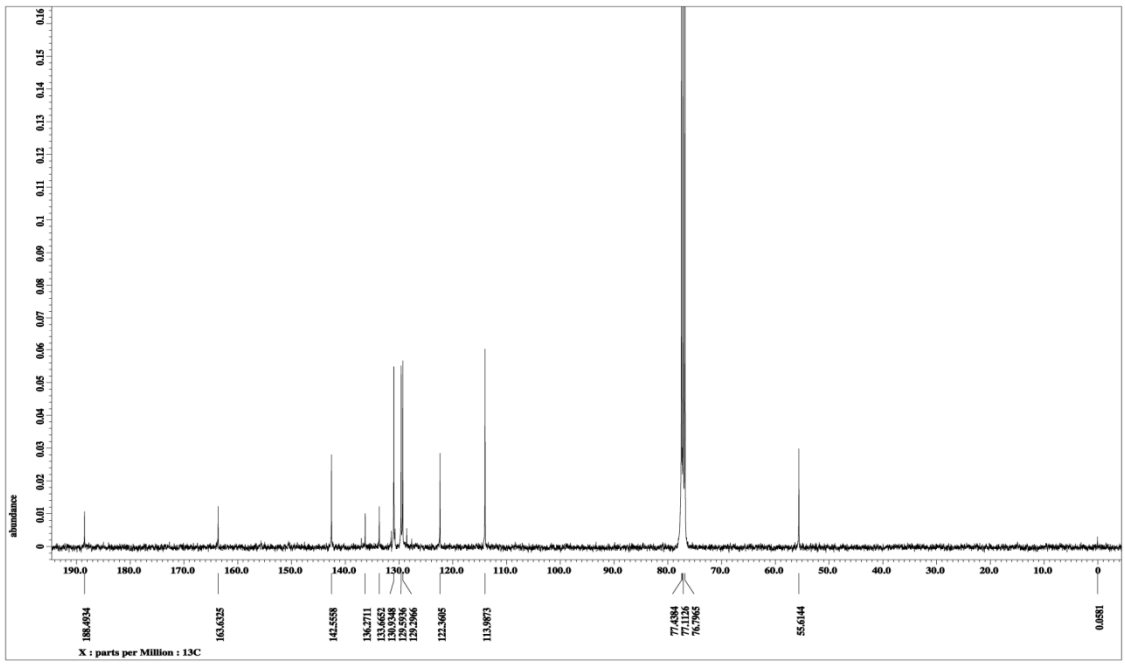




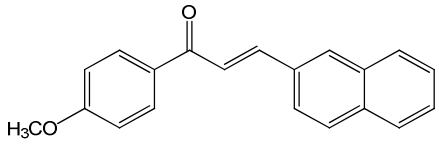
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-chlorophenyl)-1-(4-methoxyphenyl) prop-2-en-1-one MC32

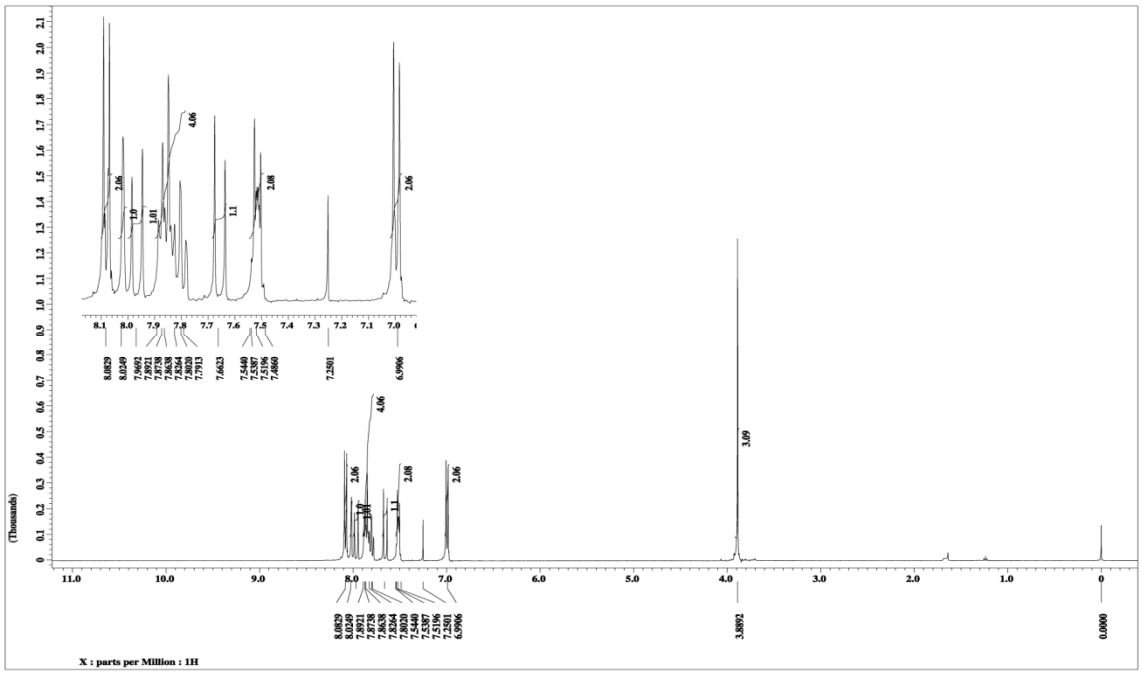


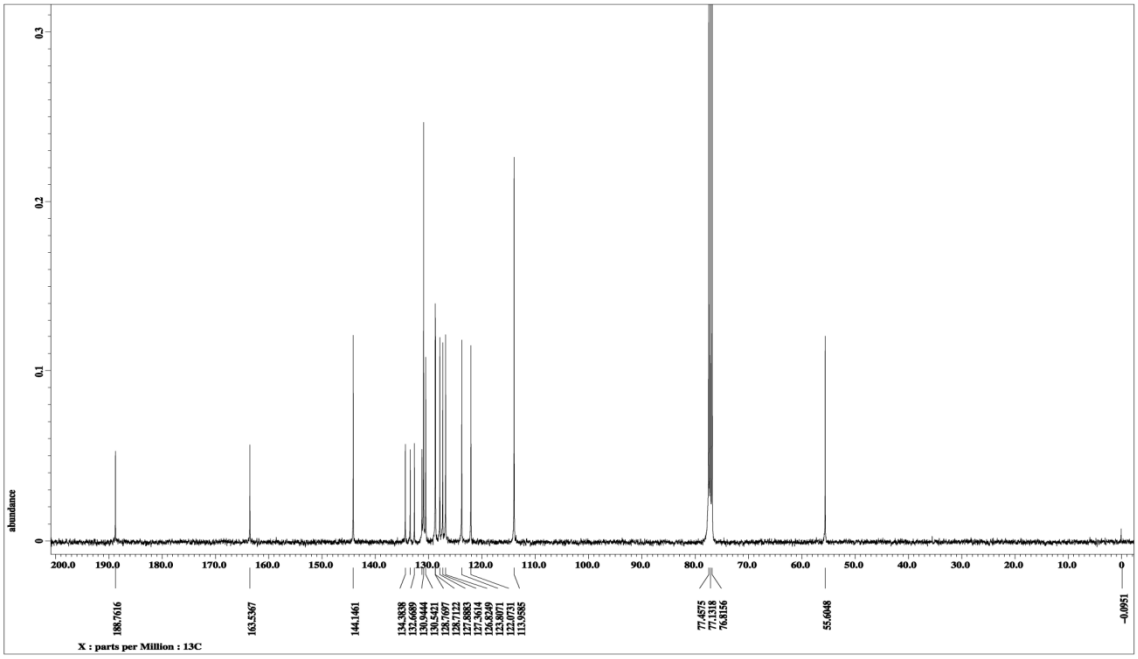




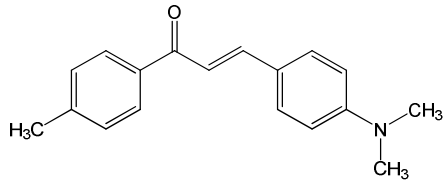
^{1}HNMR and ^{13}CNMR of (*E*)-1-(4-methoxyphenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC33

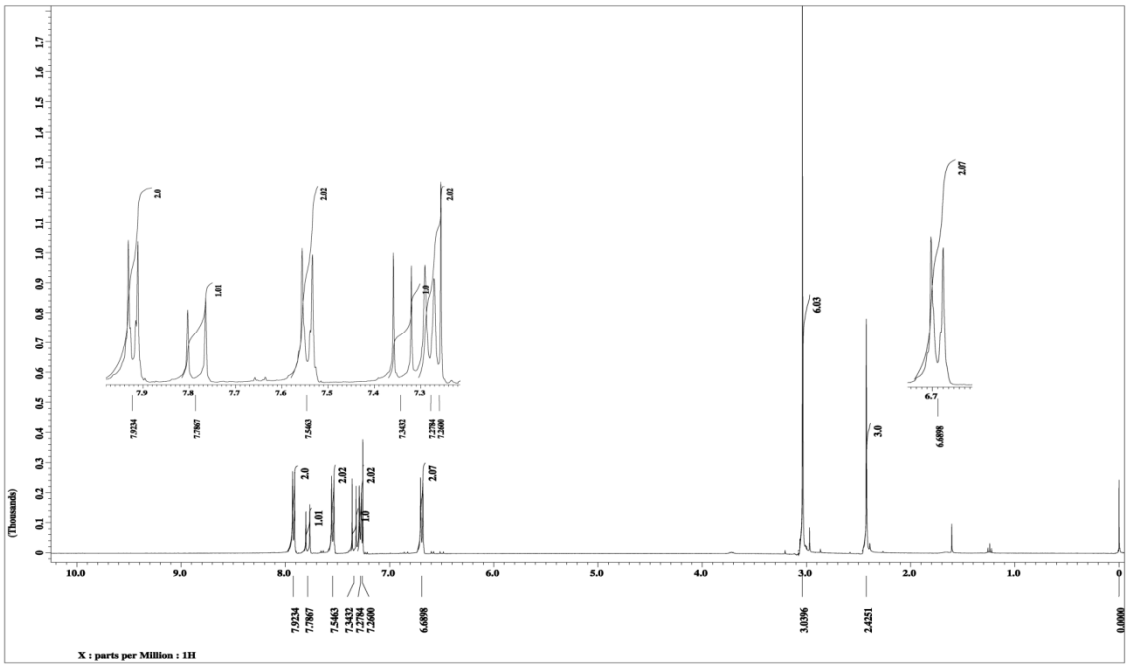


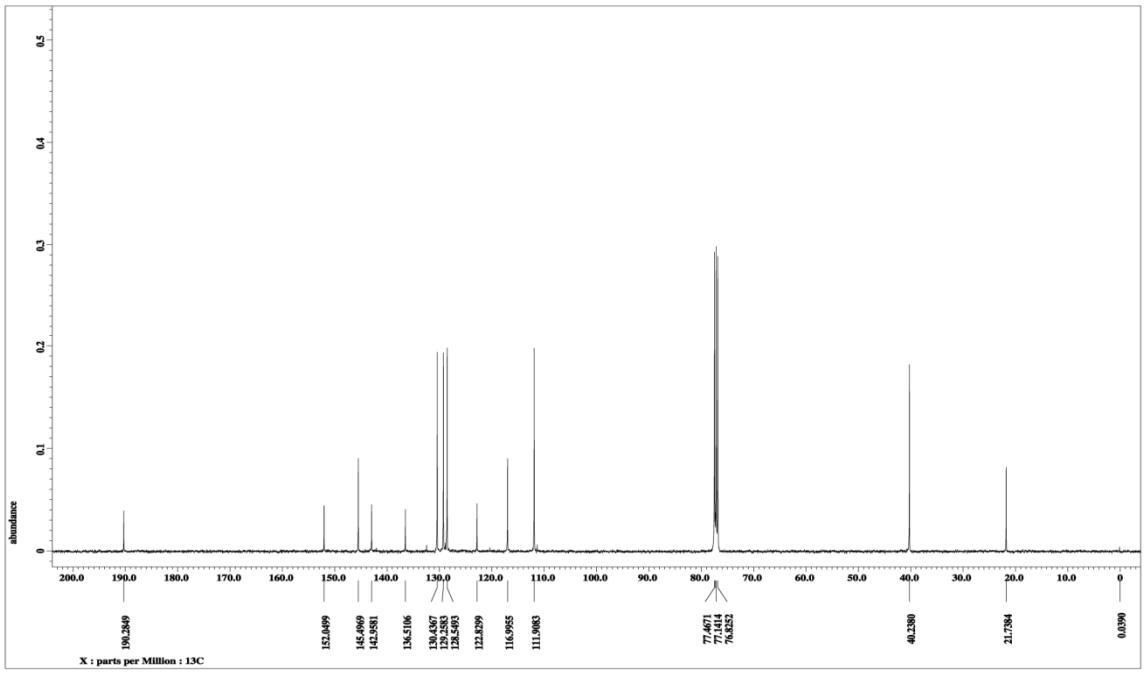




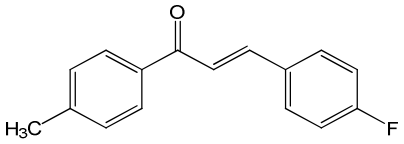
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-(dimethylamino) phenyl)-1-p-tolylprop-2-en-1-one MC34

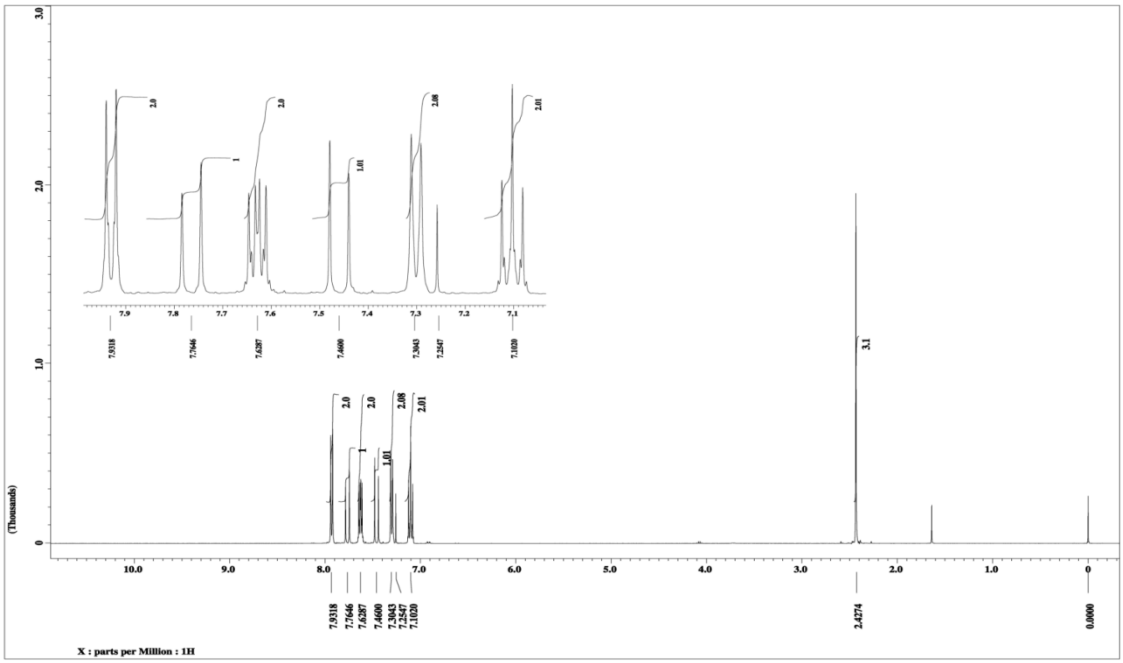


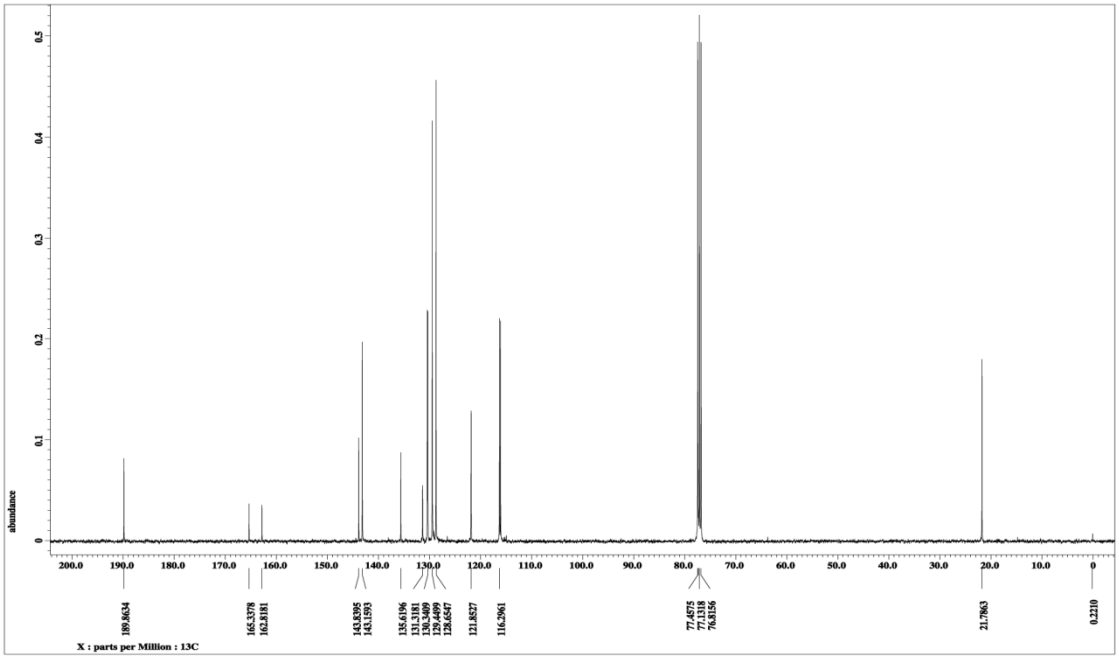




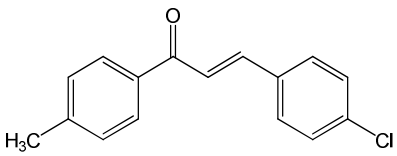
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-fluorophenyl)-1-p-tolylprop-2-en-1-one MC35

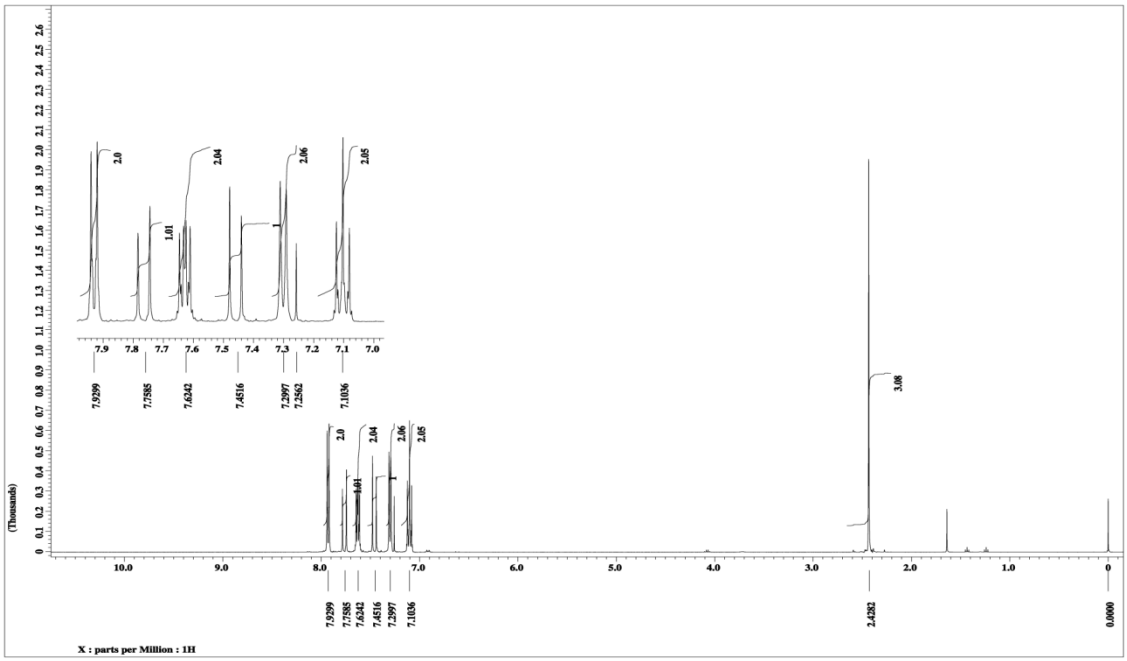


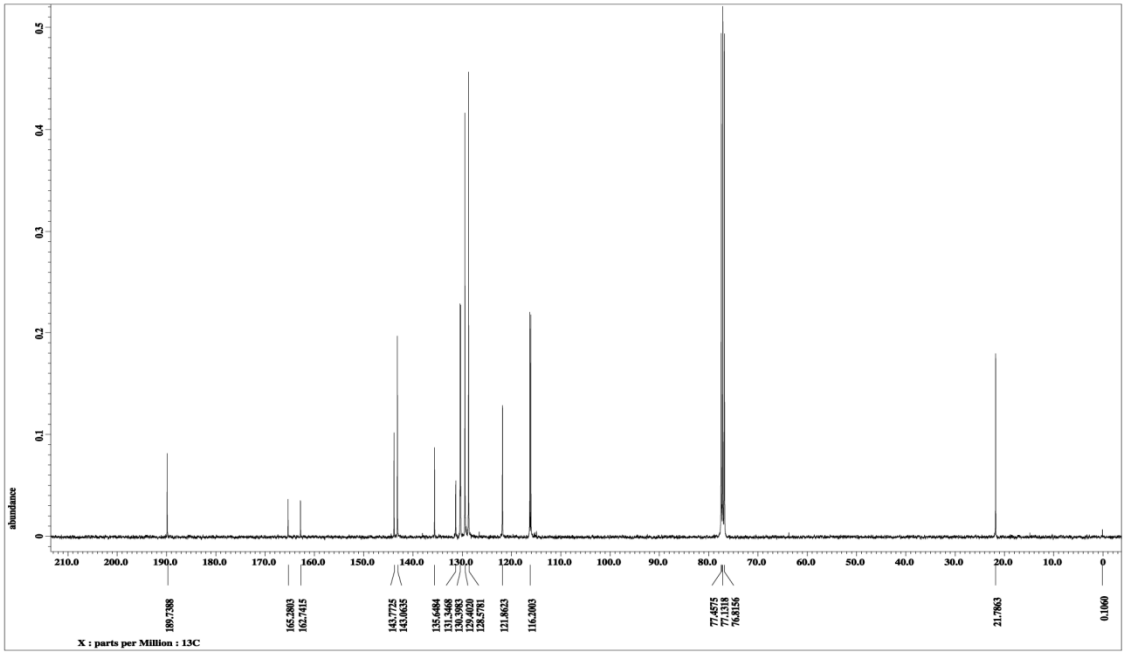




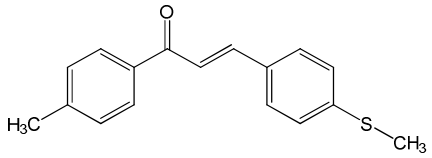
^{1}HNMR and ^{13}CNMR of (*E*)-3-(4-chlorophenyl)-1-p-tolylprop-2-en-1-one MC36

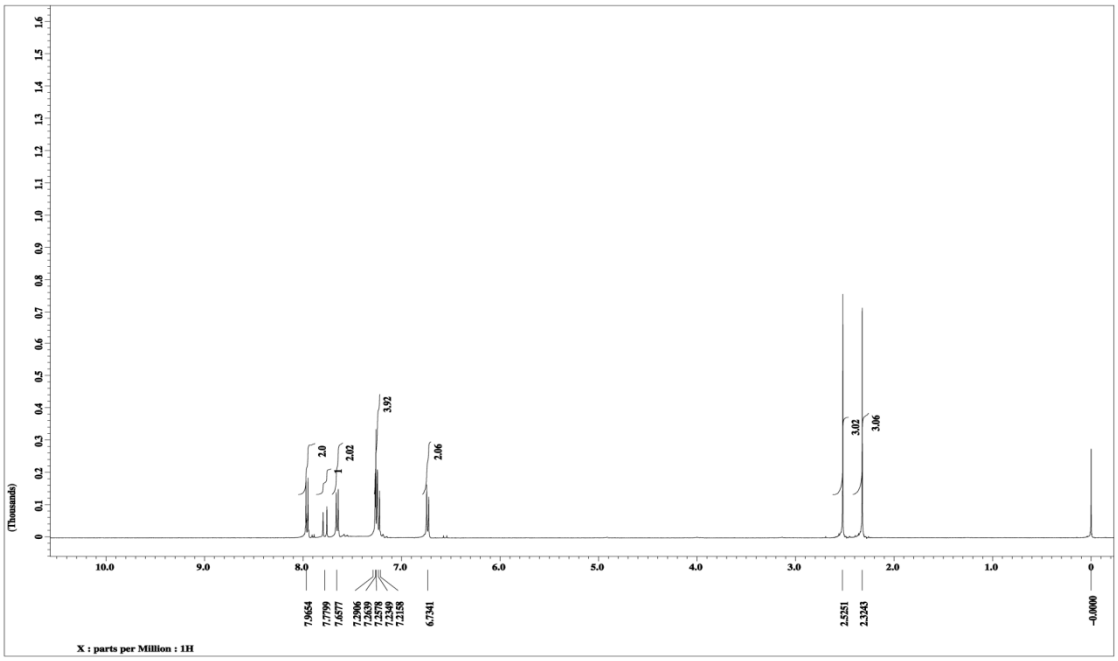


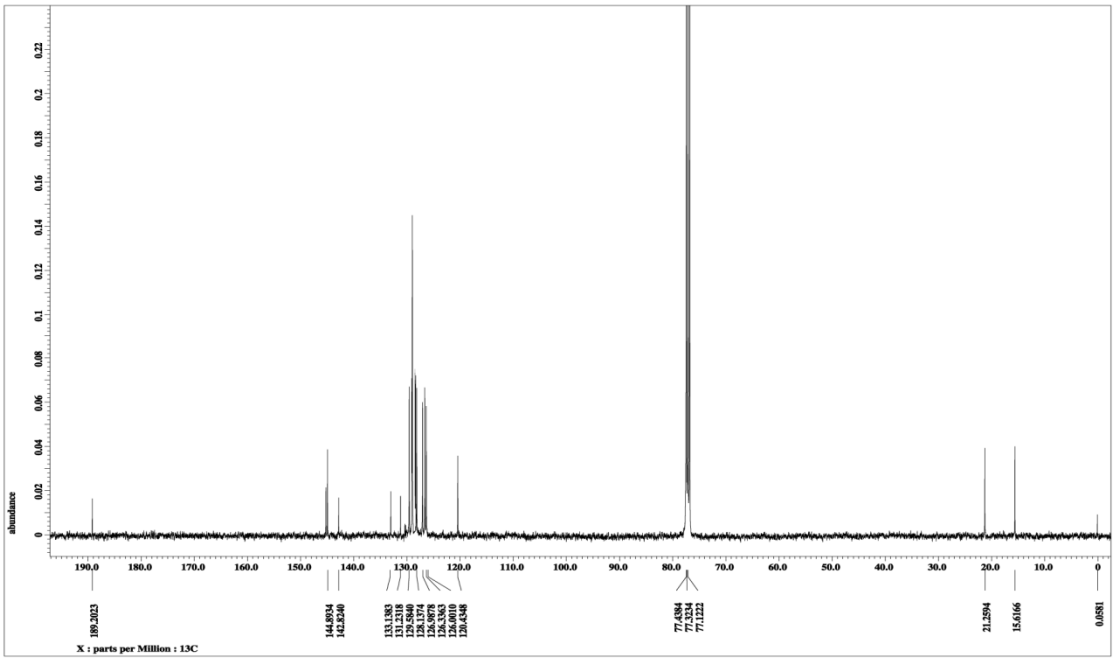




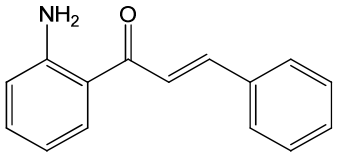
[1]HNMR and [13]CNMR of (E)-3-(4-(methylthio) phenyl)-1-p-tolylprop-2-en-1-one MC37

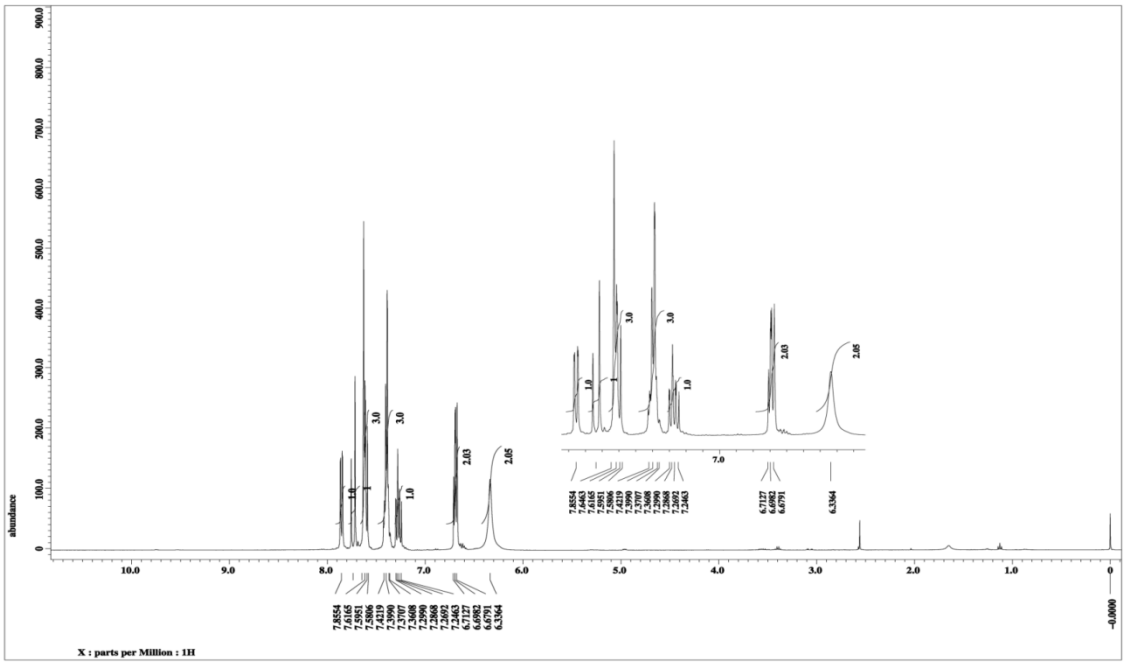


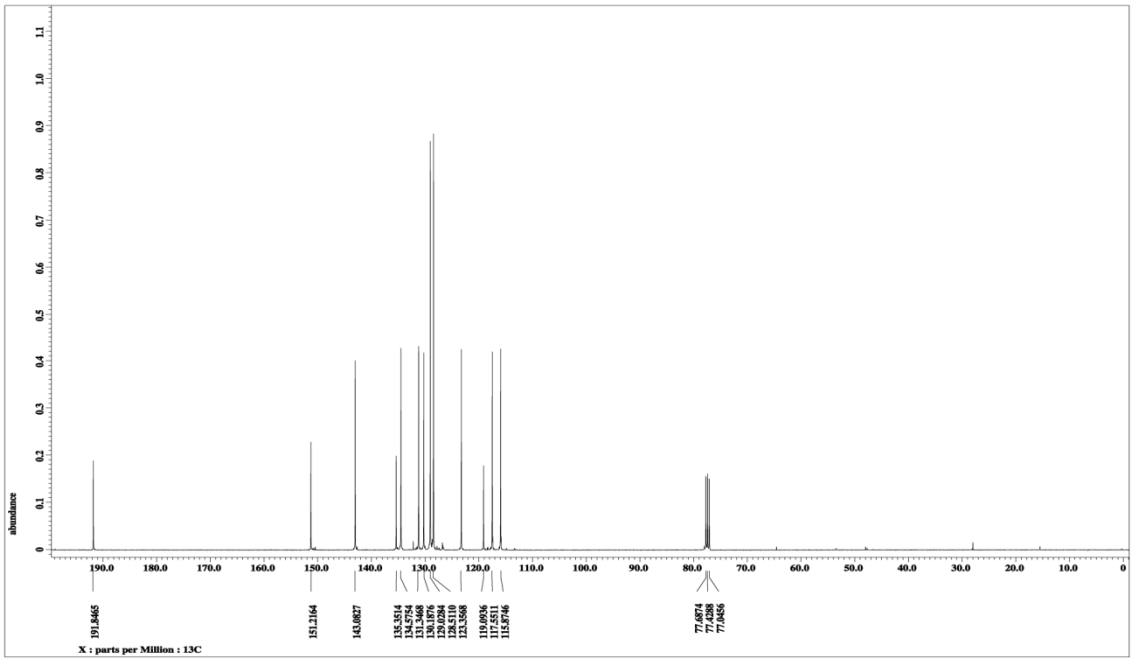




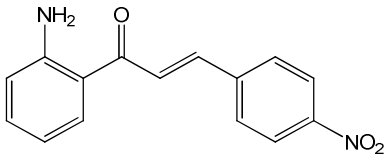
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one MC38

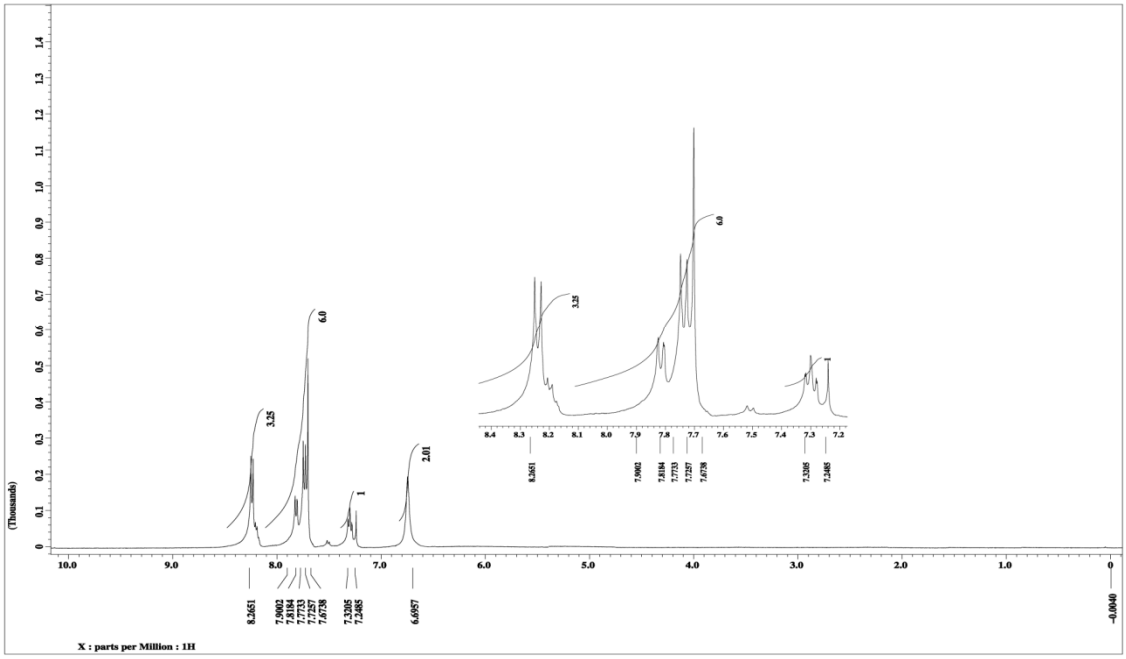


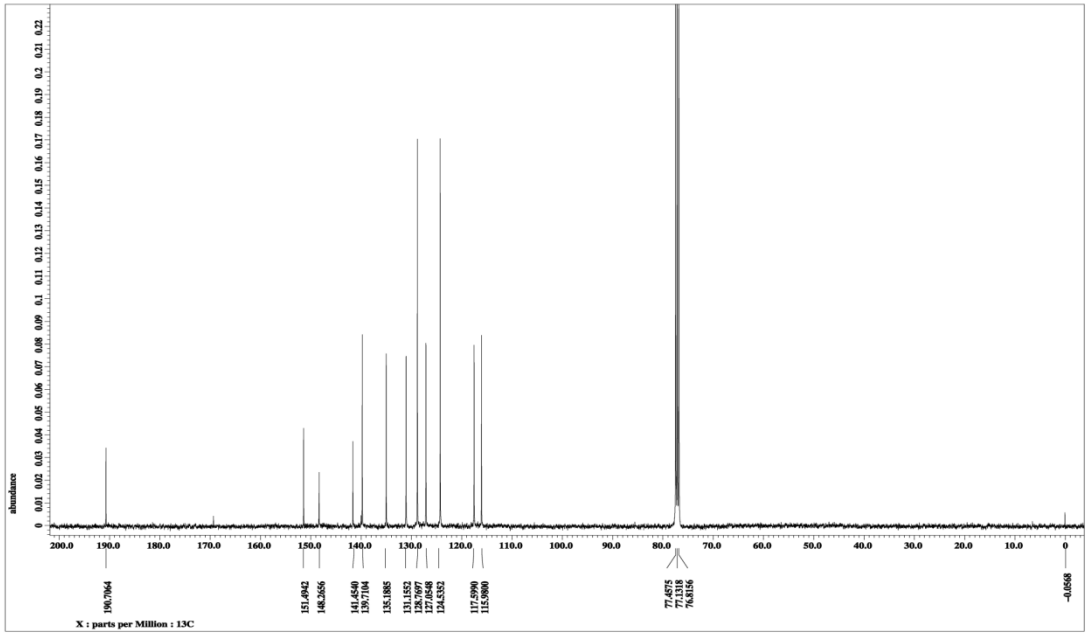




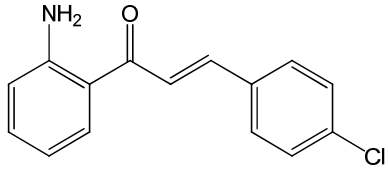
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-aminophenyl)-3-(4-nitrophenyl) prop-2-en-1-one MC39

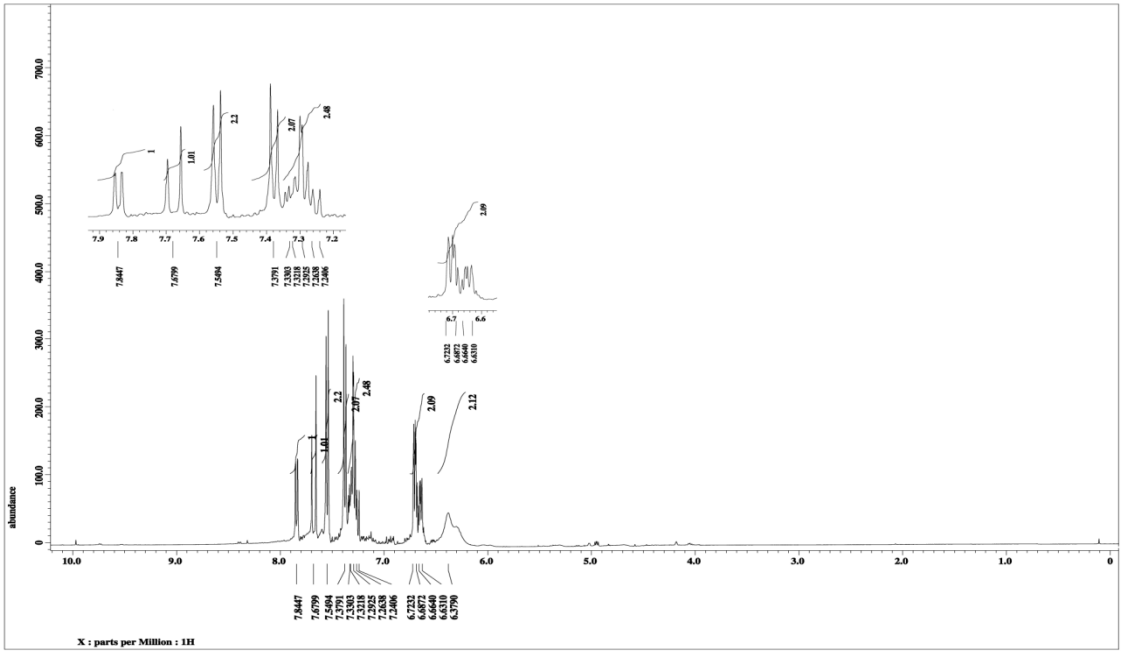


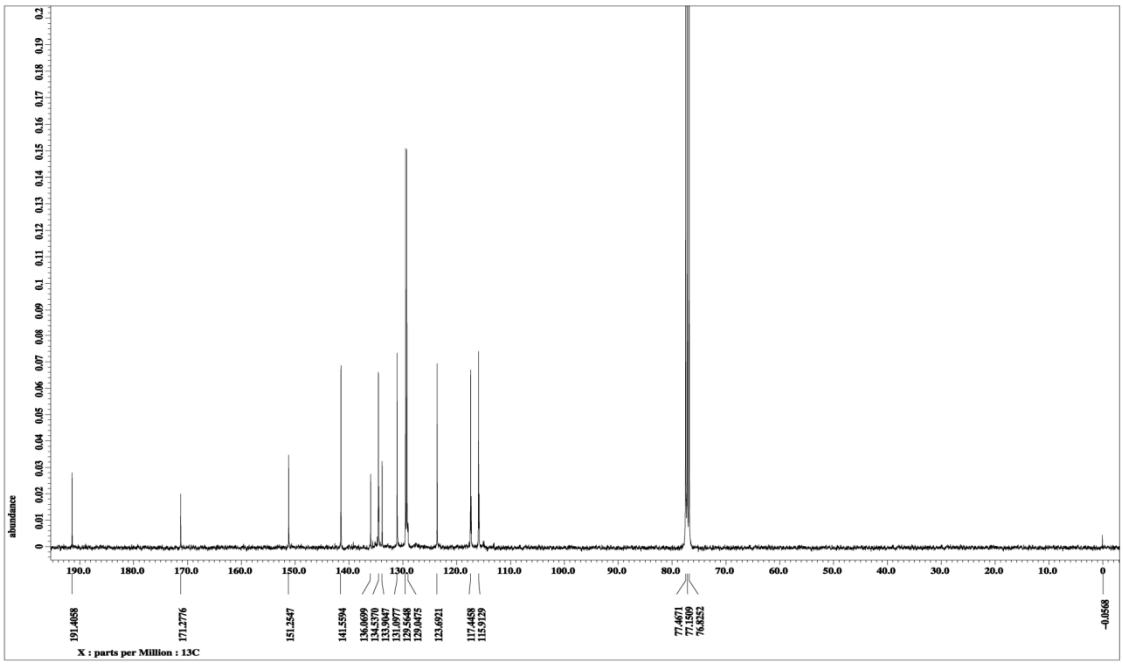




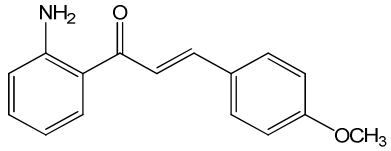
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-aminophenyl)-3-(4-chlorophenyl) prop-2-en-1-one MC40

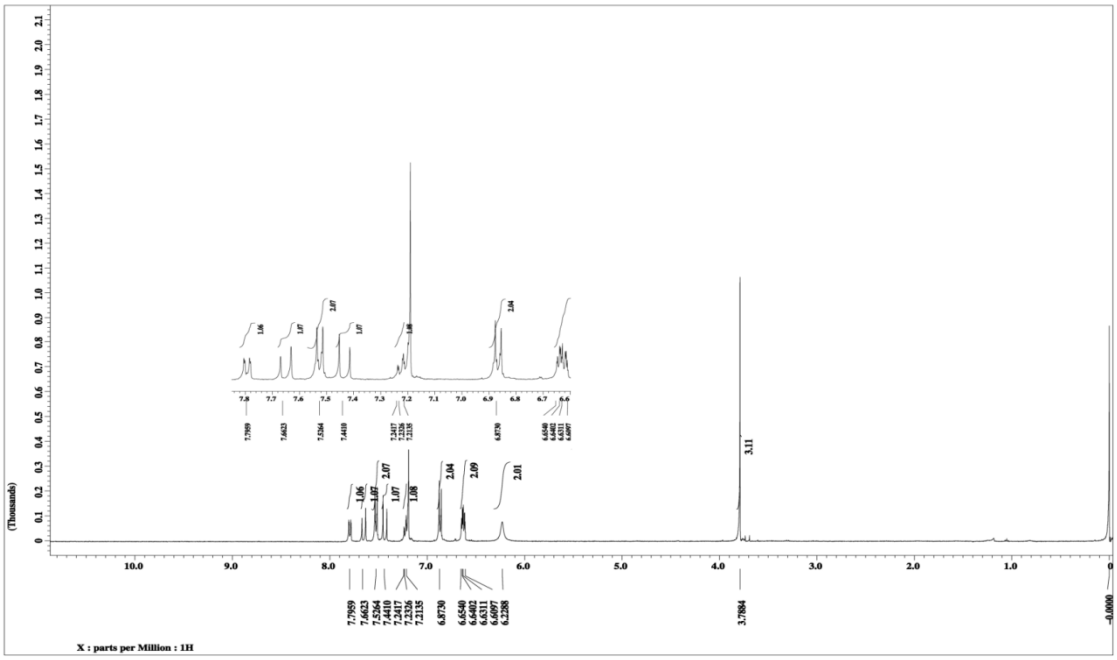


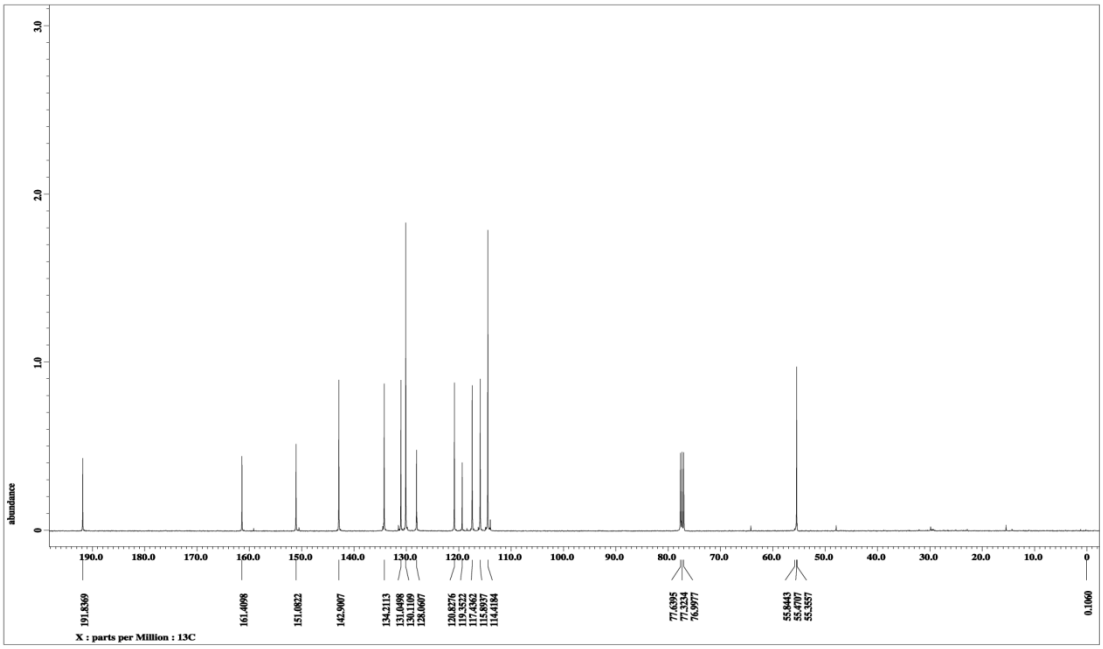




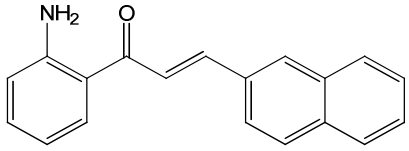
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-aminophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one MC41

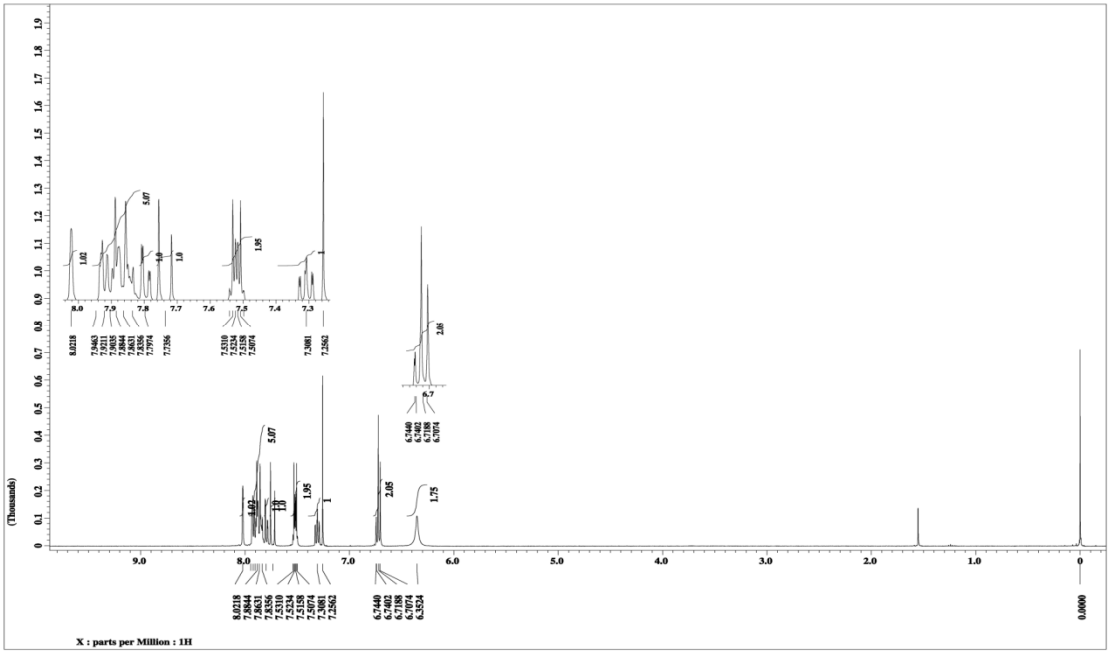


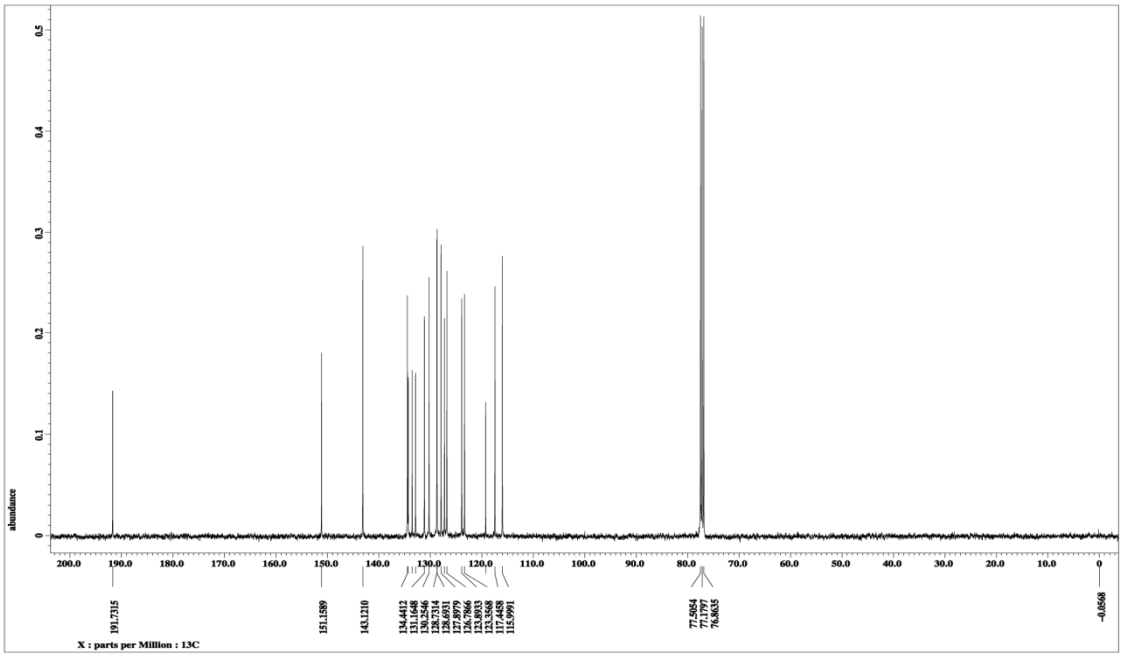




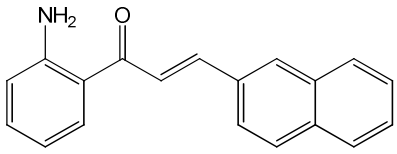
^{1}HNMR and ^{13}CNMR of (*E*)-1-(2-aminophenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC42

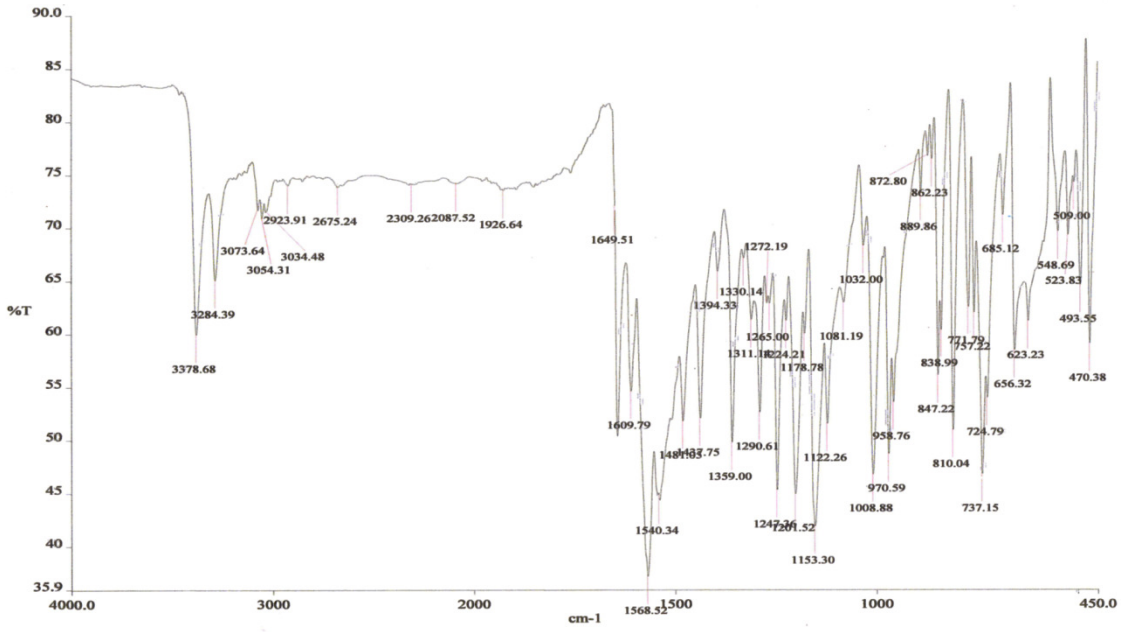




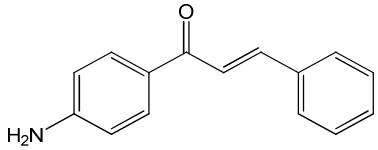


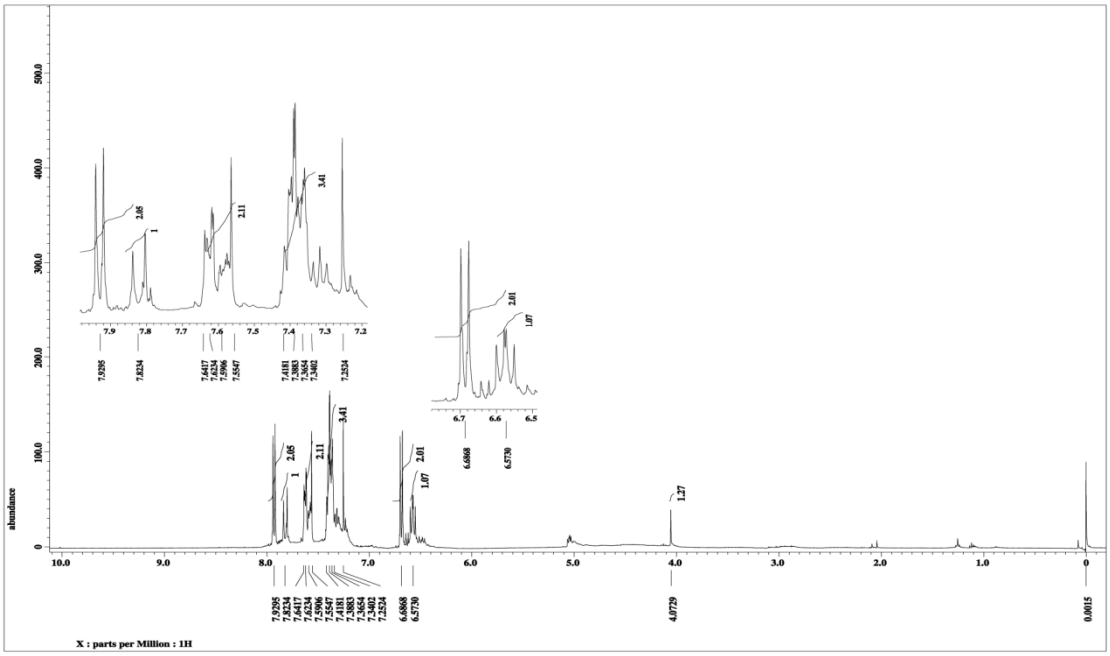
IR of (*E*)-1-(2-aminophenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC42

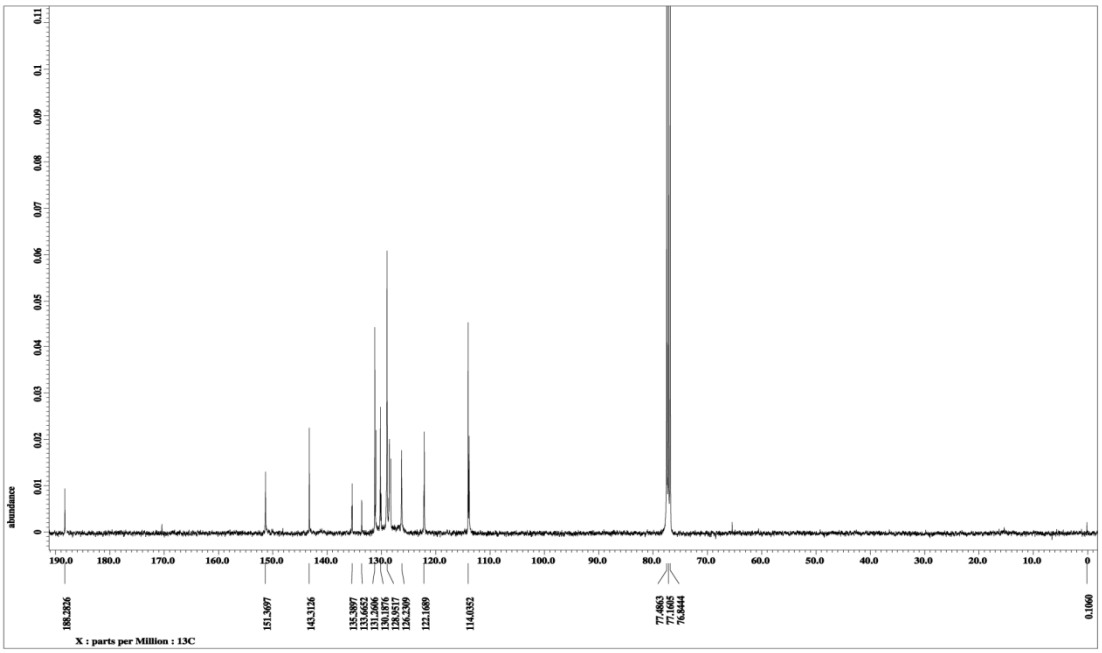




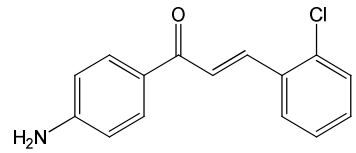
^{1}HNMR and ^{13}CNMR of (*E*)-1-(4-aminophenyl)-3-phenylprop-2-en-1-one MC43

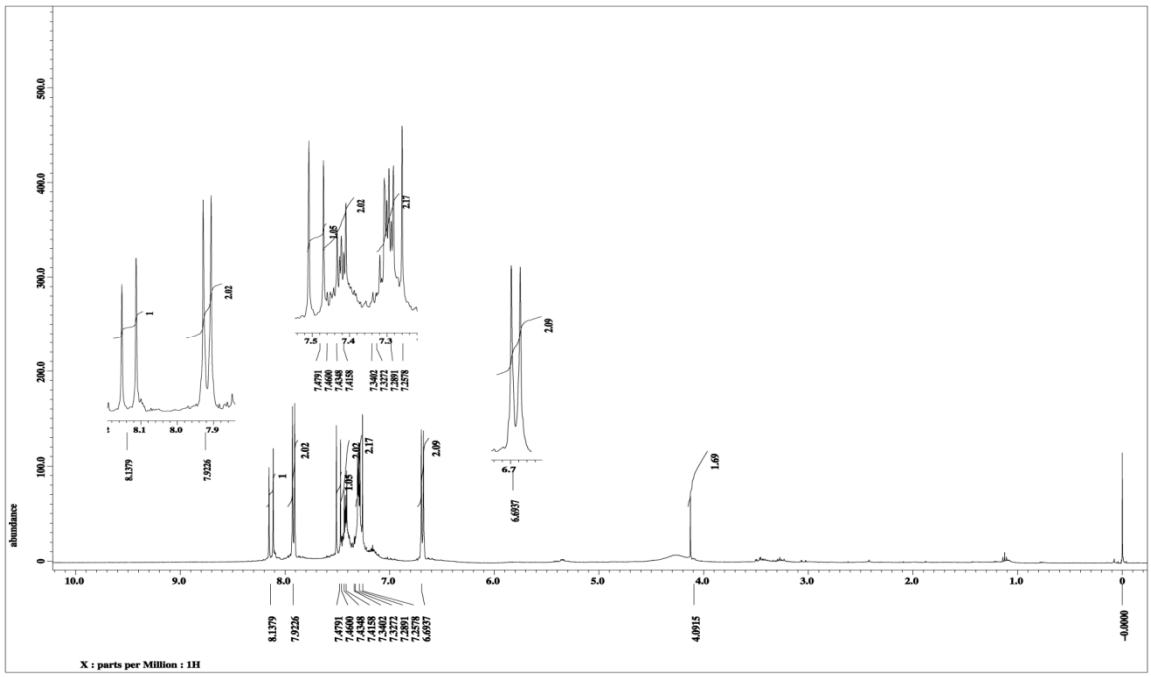


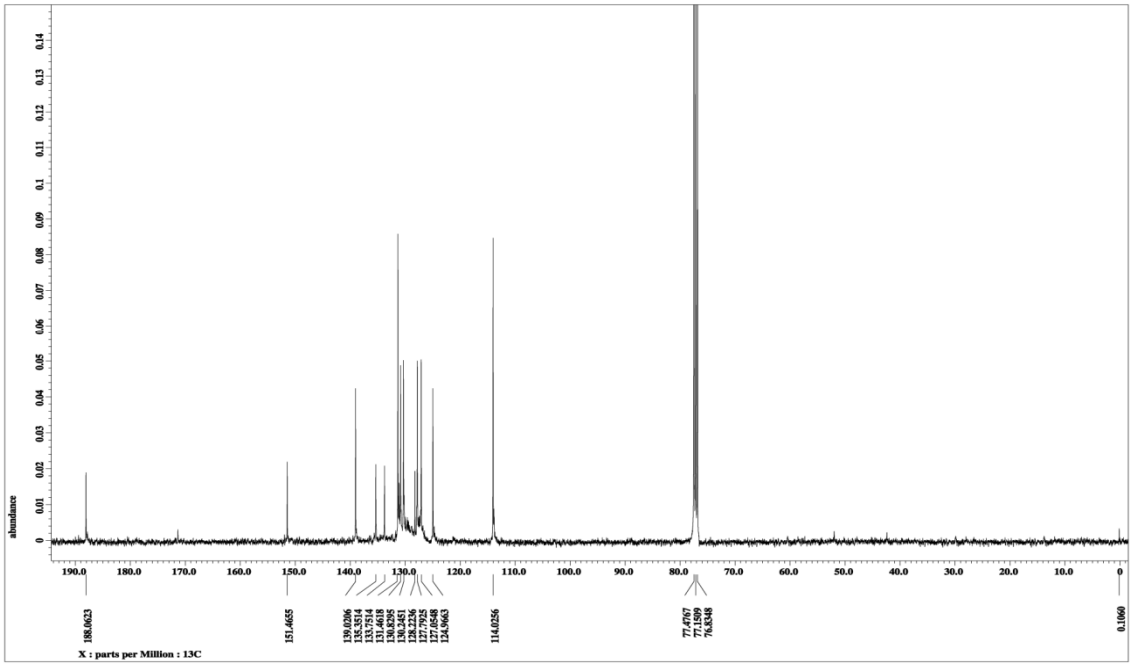




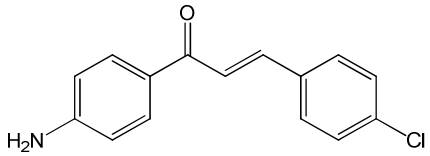
[1]HNMR and [13]CNMR of (*E*)-1-(4-aminophenyl)-3-(2-chlorophenyl) prop-2-en-1-one MC44

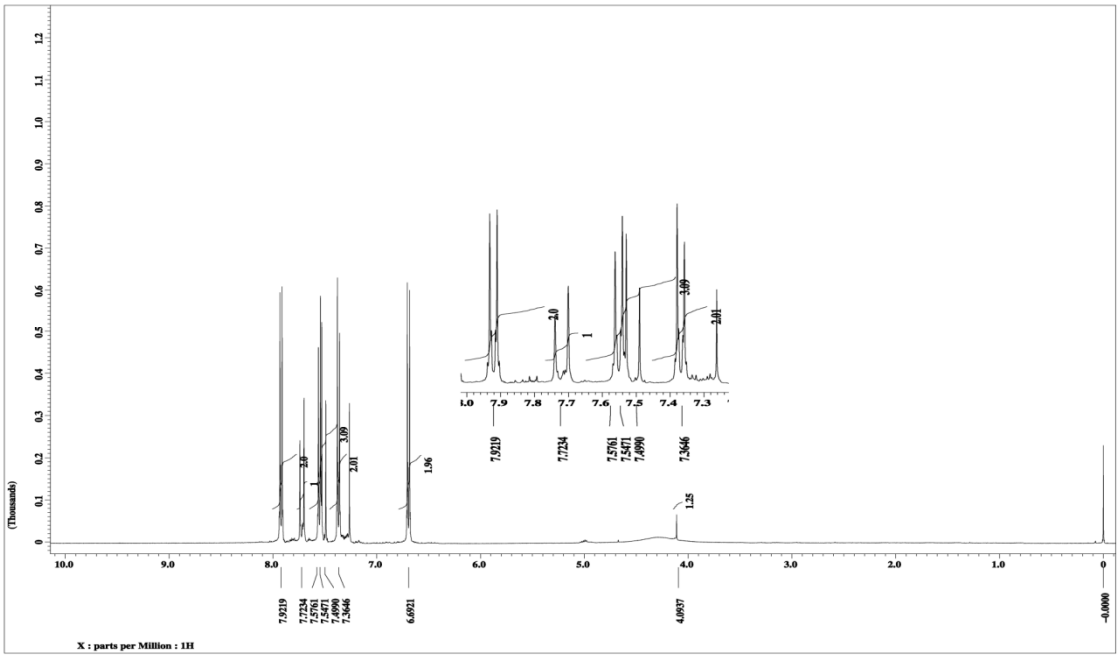


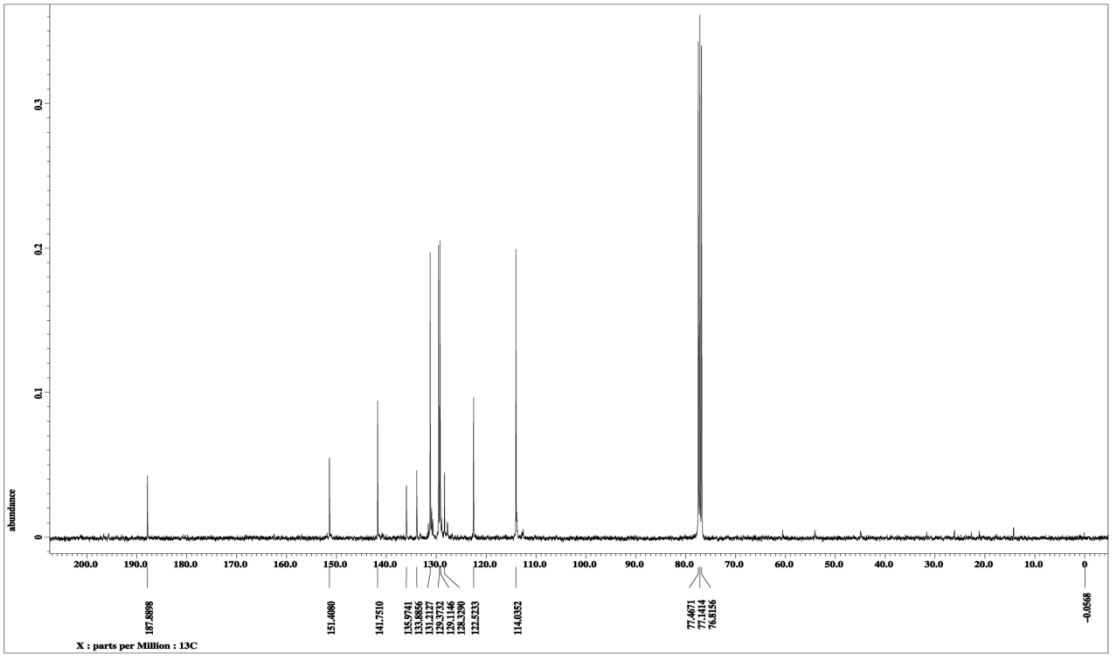




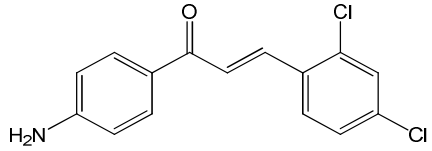
^{1}HNMR and ^{13}CNMR of (*E*)-1-(4-aminophenyl)-3-(4-chlorophenyl) prop-2-en-1-one MC45

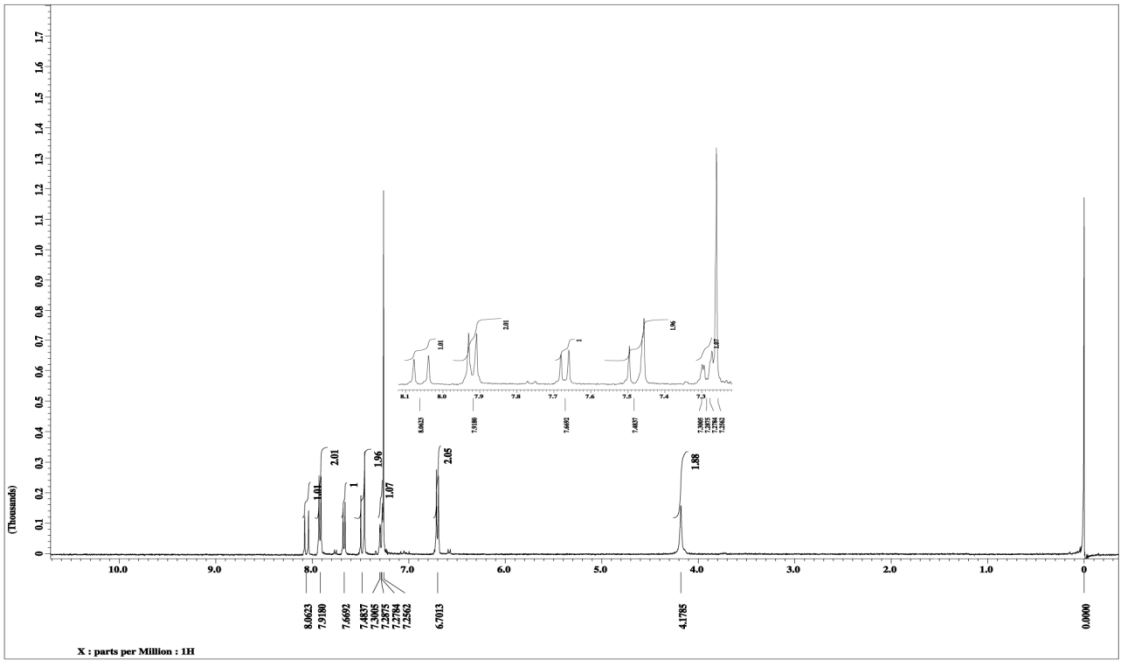


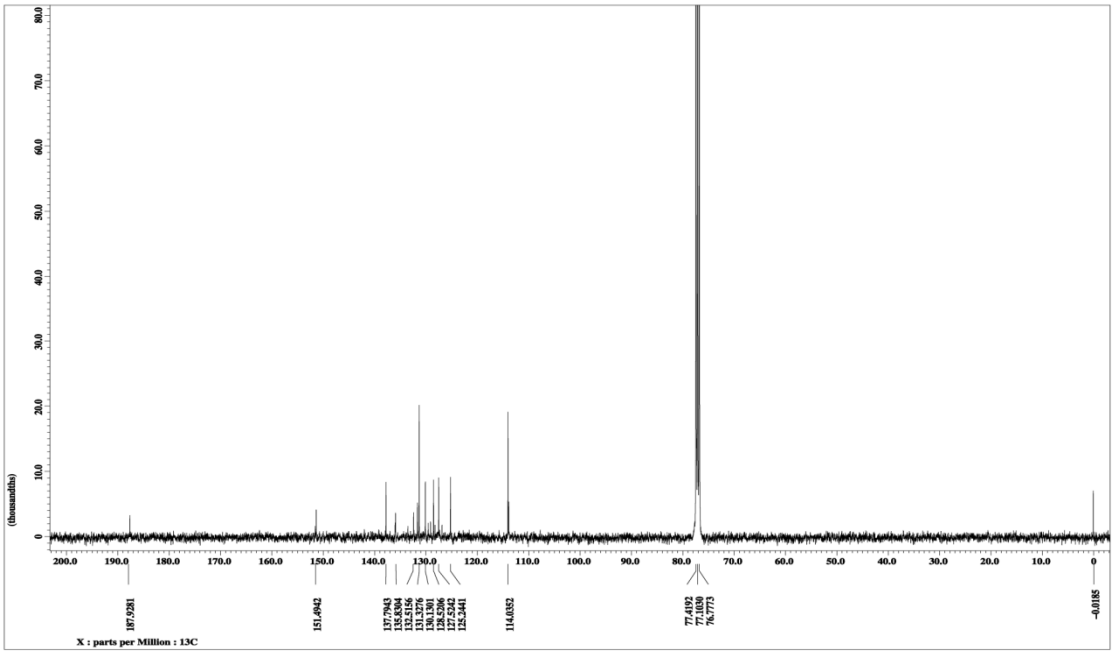




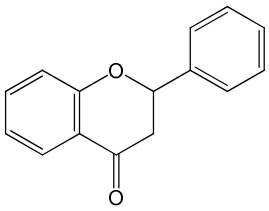
^{1}HNMR and ^{13}CNMR of (*E*)-1-(4-aminophenyl)-3-(2, 4-dichlorophenyl)prop-2-en-1-one MC46

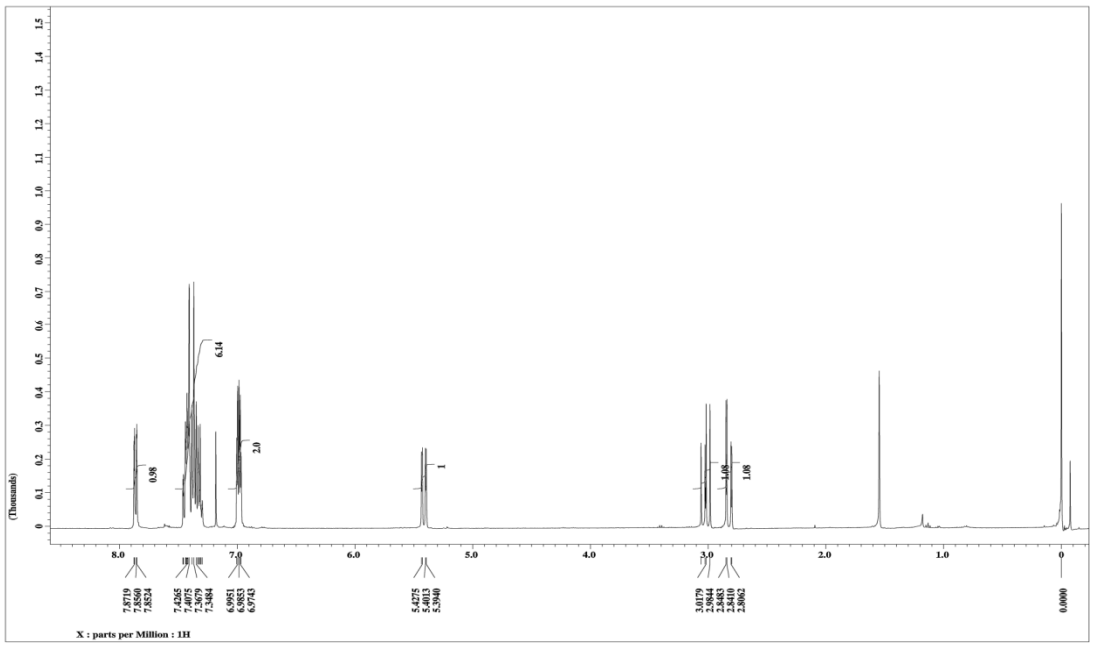


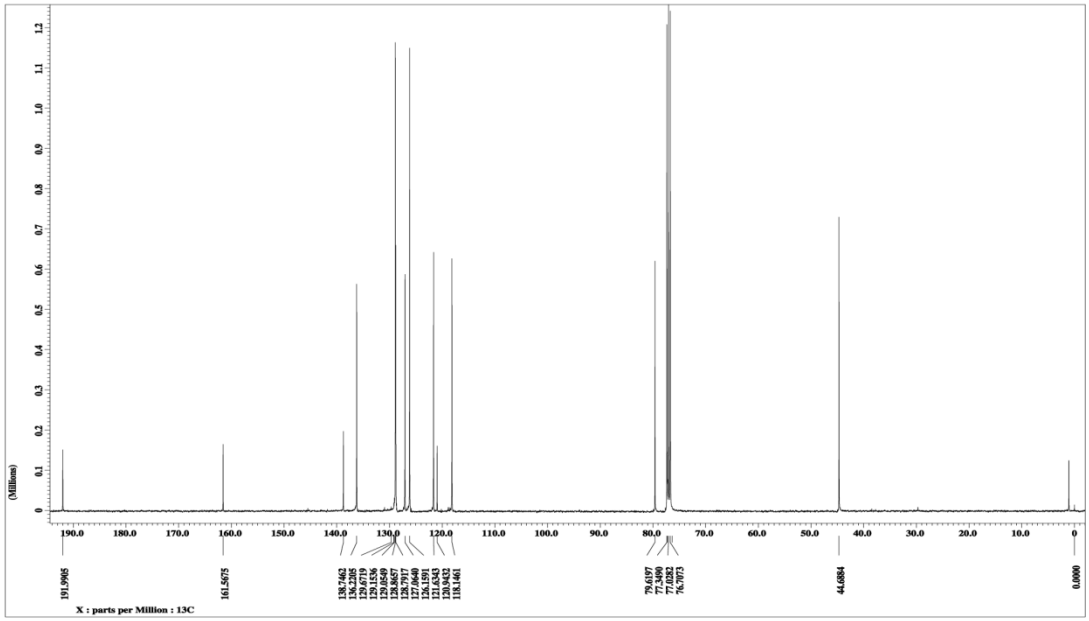




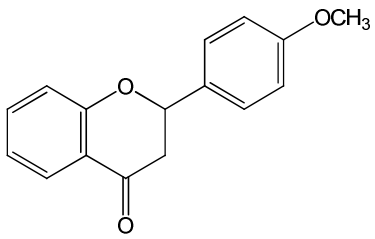
[1]HNMR and [13]CNMR of 2-phenylchroman-4-one MF1

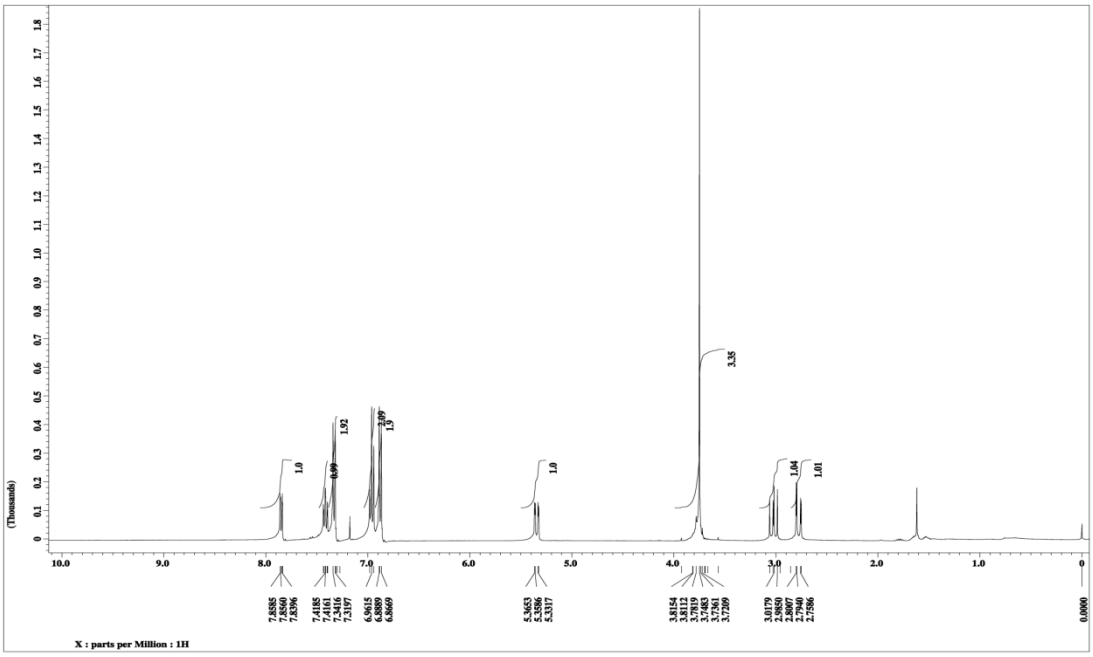


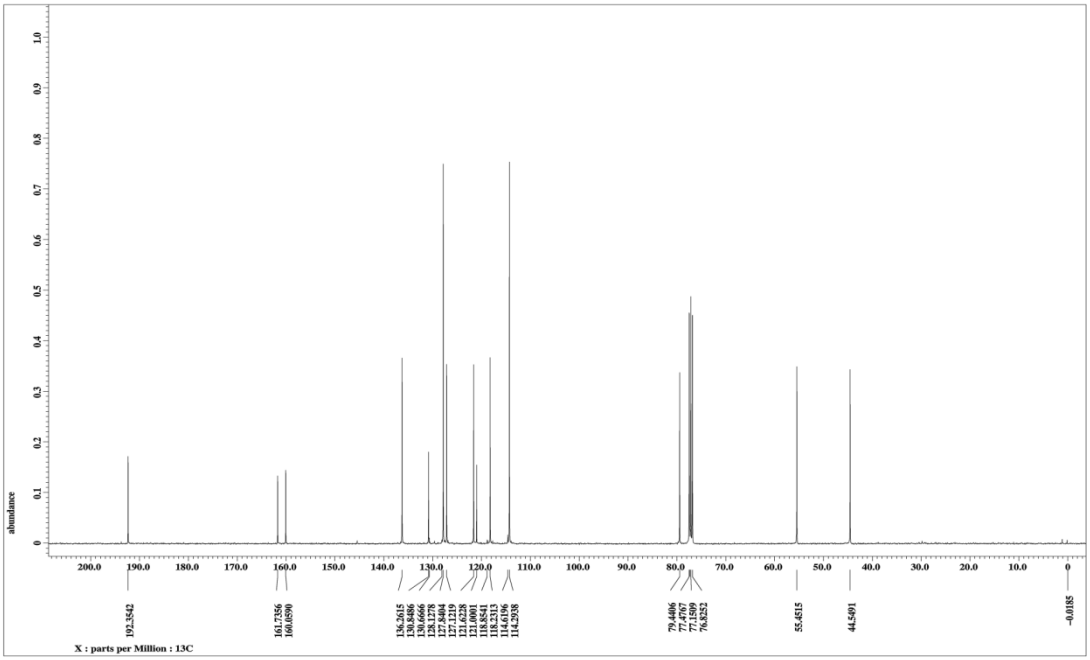




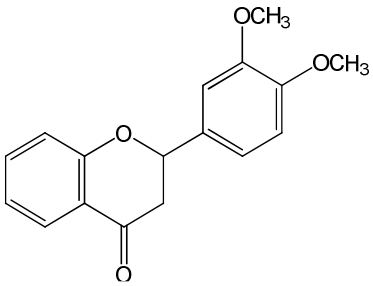
[1]HNMR and [13]CNMR of 2- (4-methoxyphenyl) chroman-4-one MF2

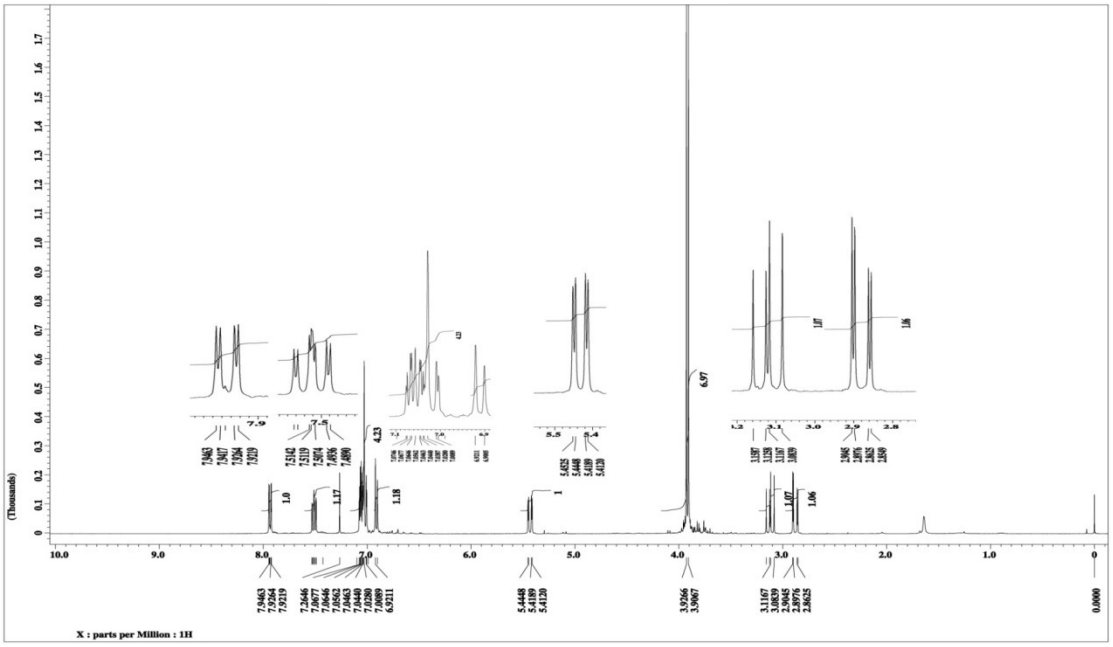


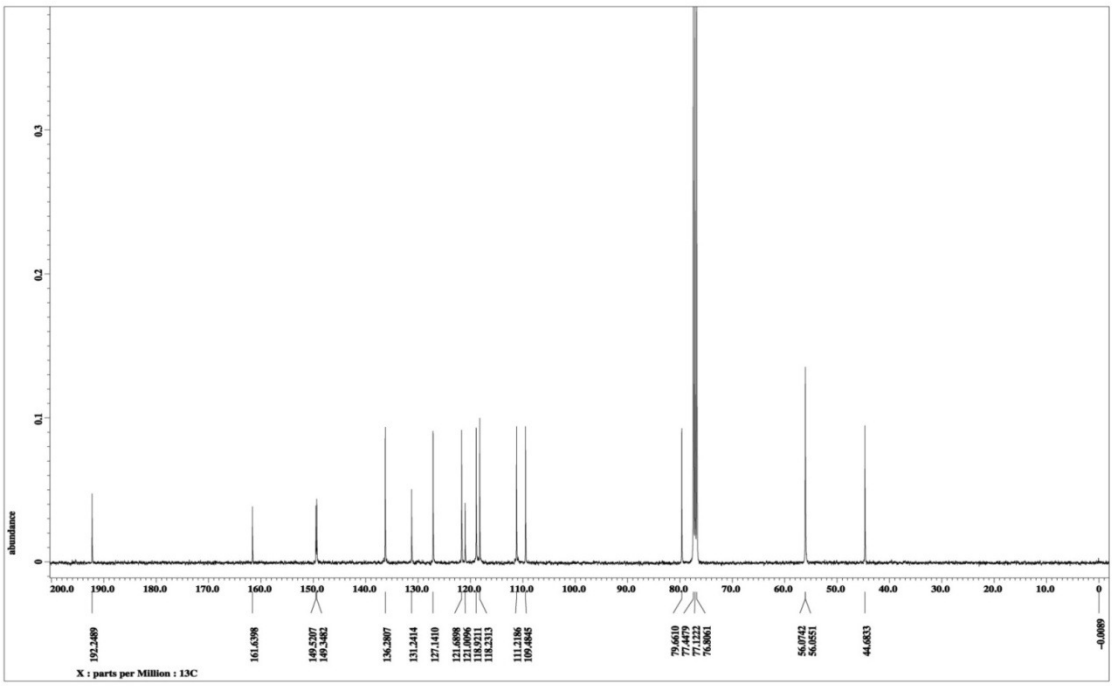




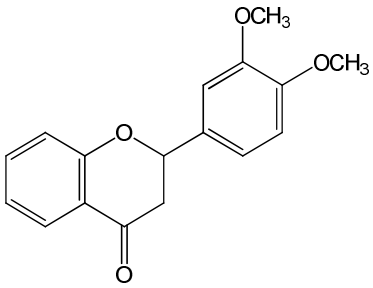
^{1}HNMR and ^{13}CNMR of 2- (3, 4- dimethoxyphenyl) chroman-4-one MF3

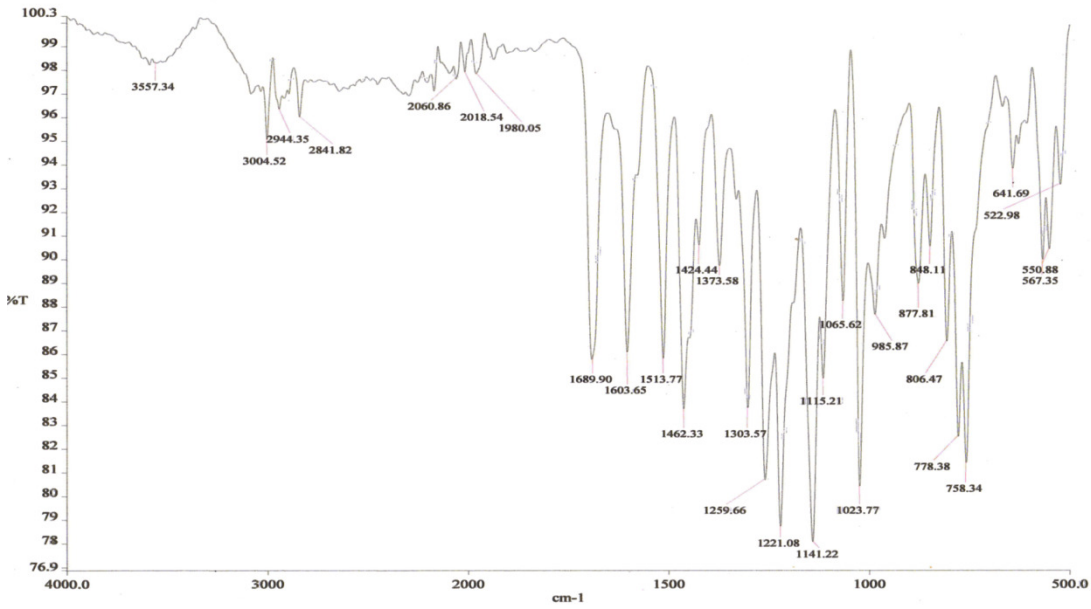




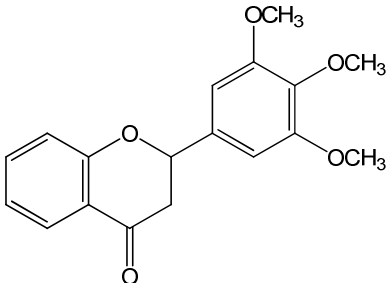


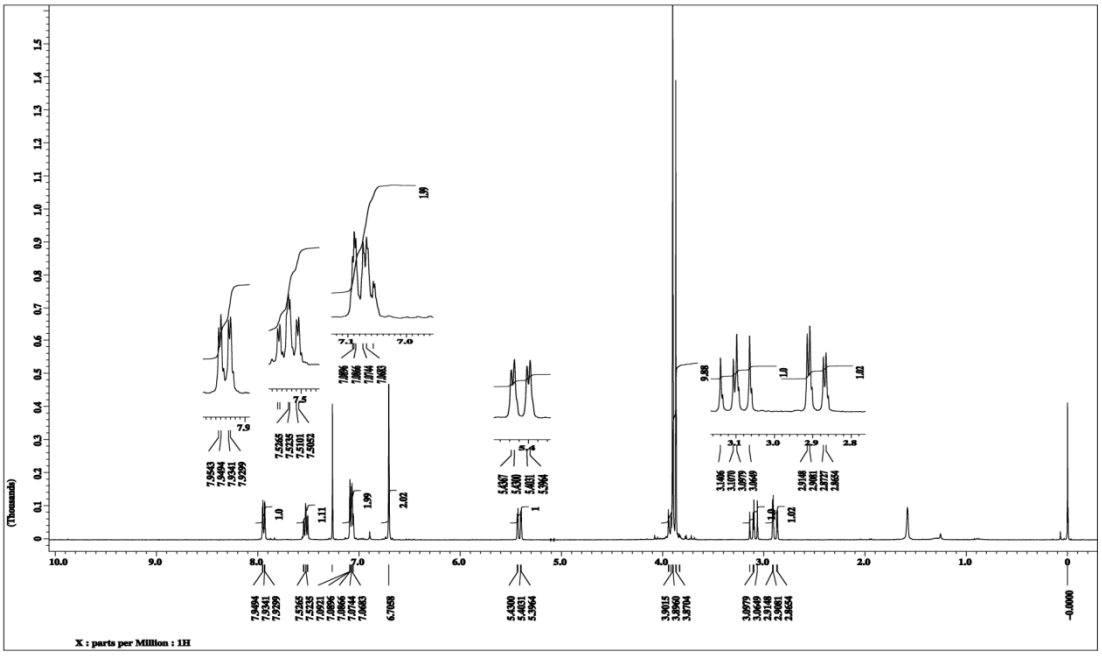
IR of 2- (3, 4- dimethoxyphenyl) chroman-4-one MF3

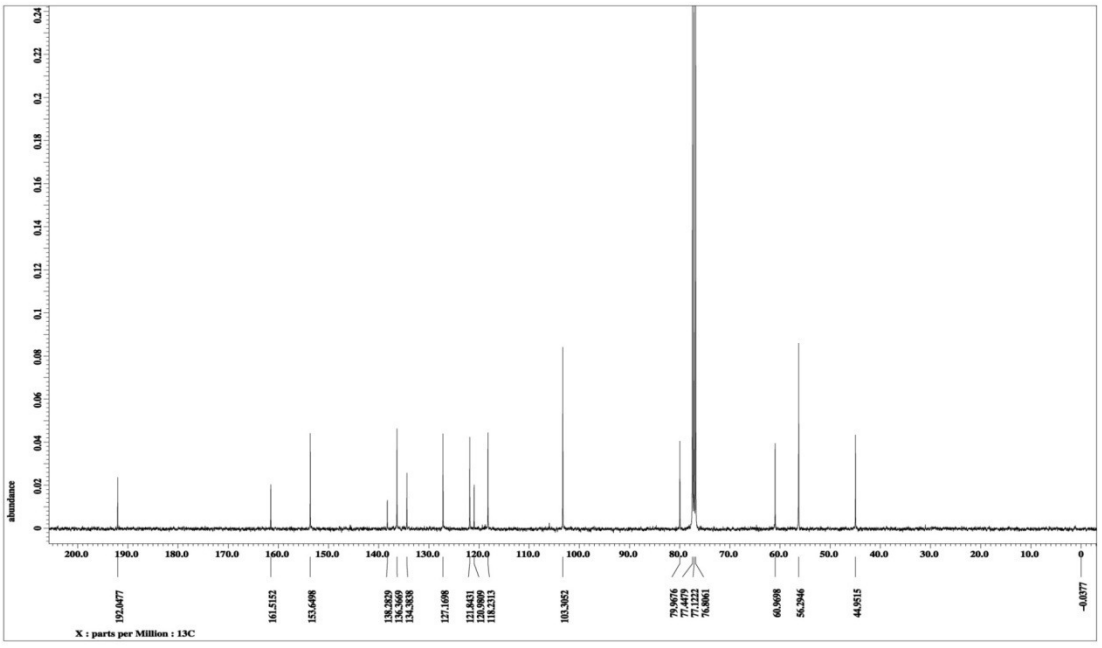




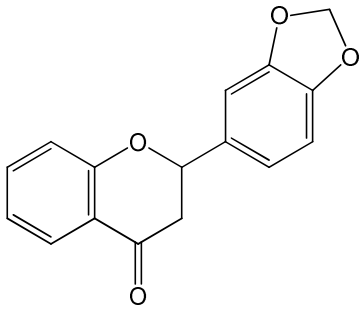
^{1}HNMR and ^{13}CNMR of 2- (3, 4, 5- trimethoxyphenyl) chroman-4-one MF4

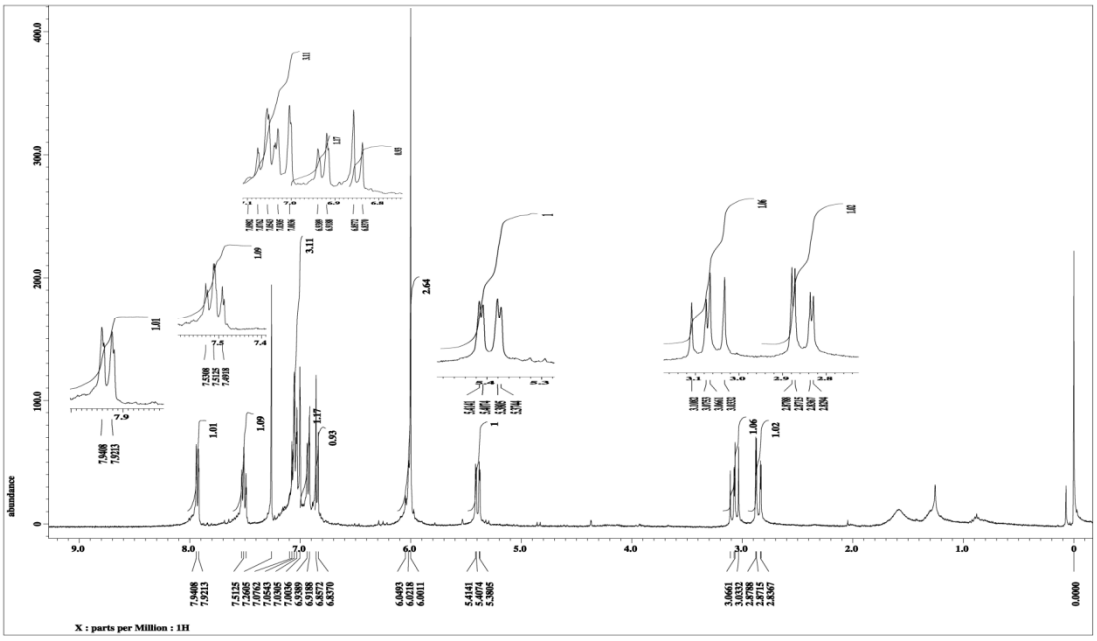


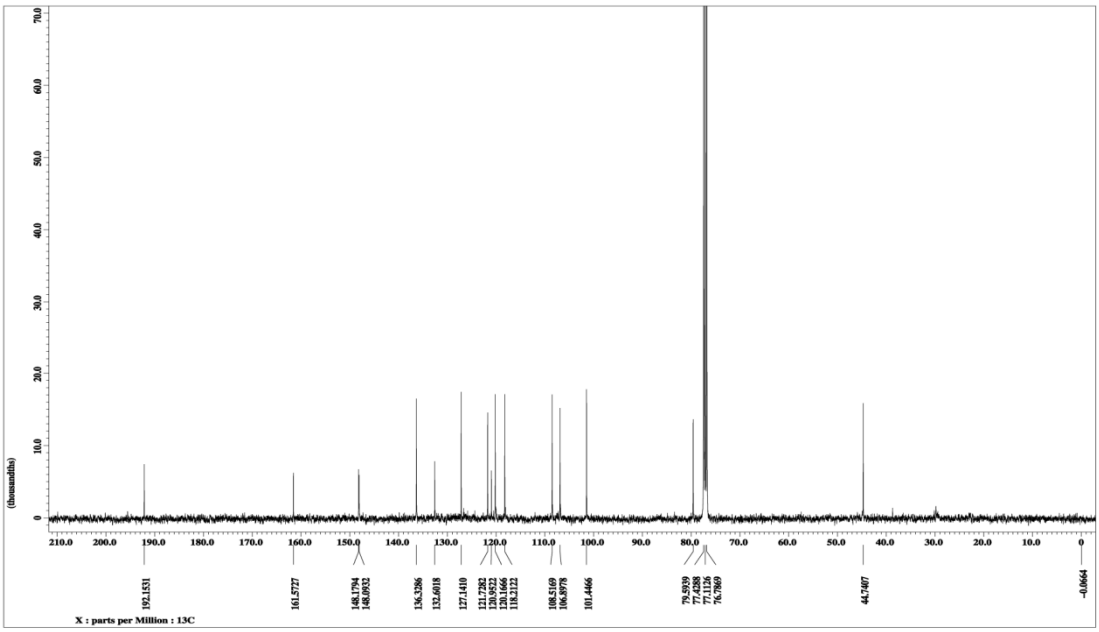




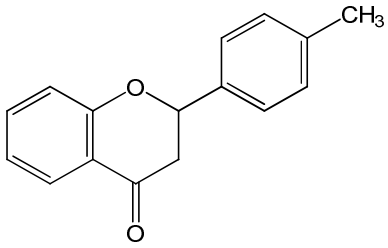
^{1}HNMR and ^{13}CNMR of 2- (benzo [*d*][1, 3] dioxol-5-yl) chroman-4-one MF5

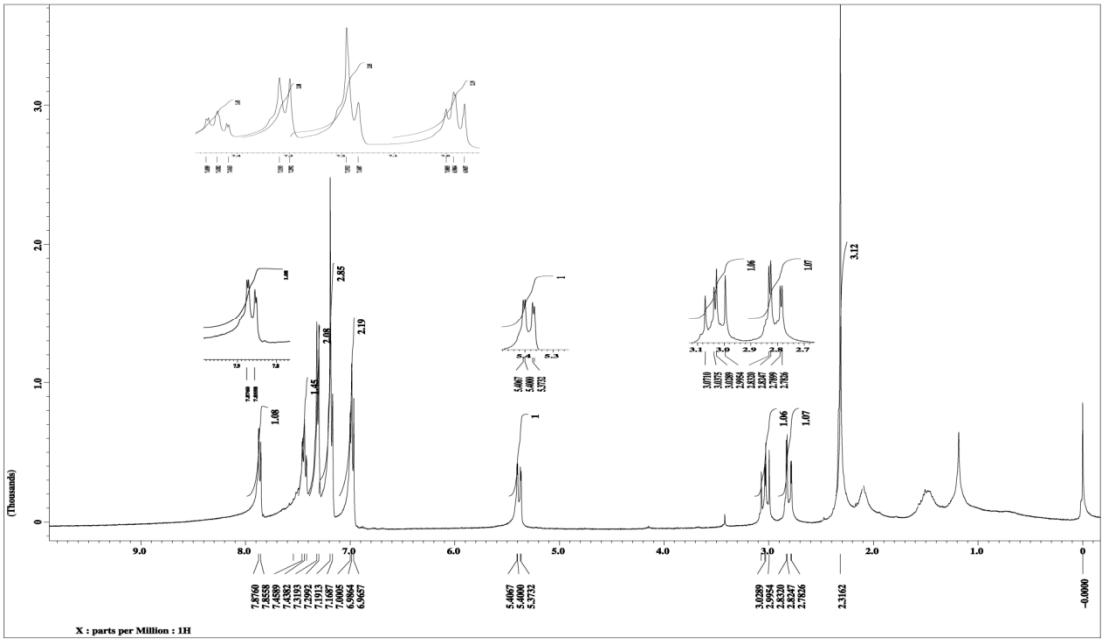


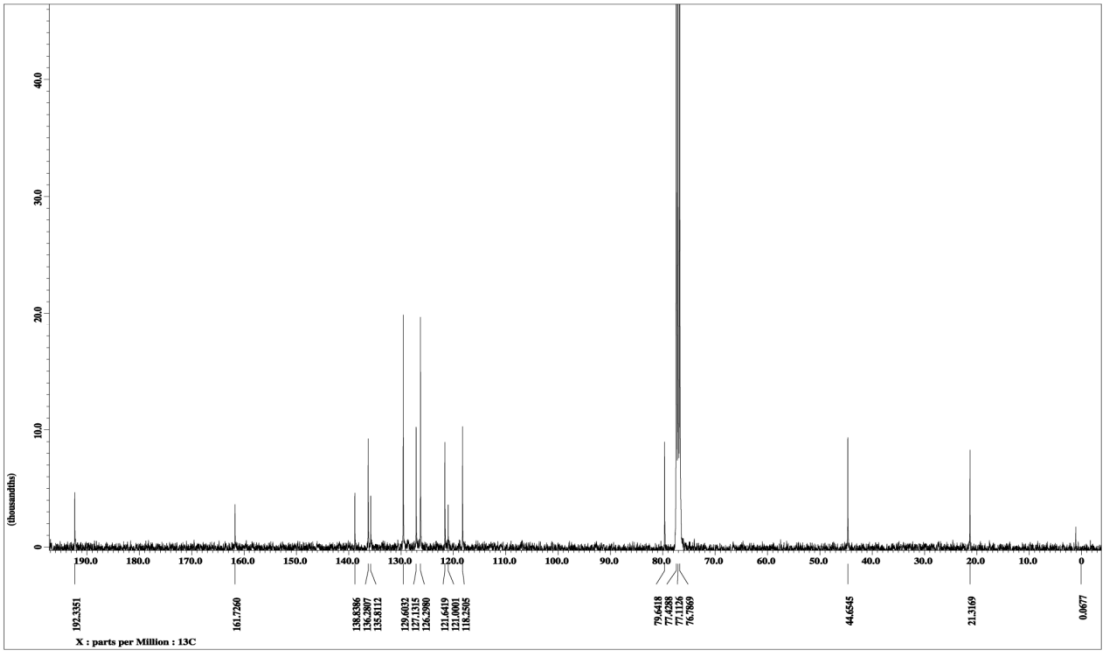




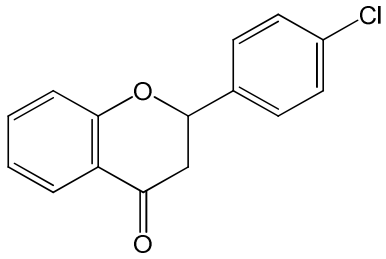
^{1}HNMR and ^{13}CNMR of 2-*p*- tolylchroman-4-one MF6

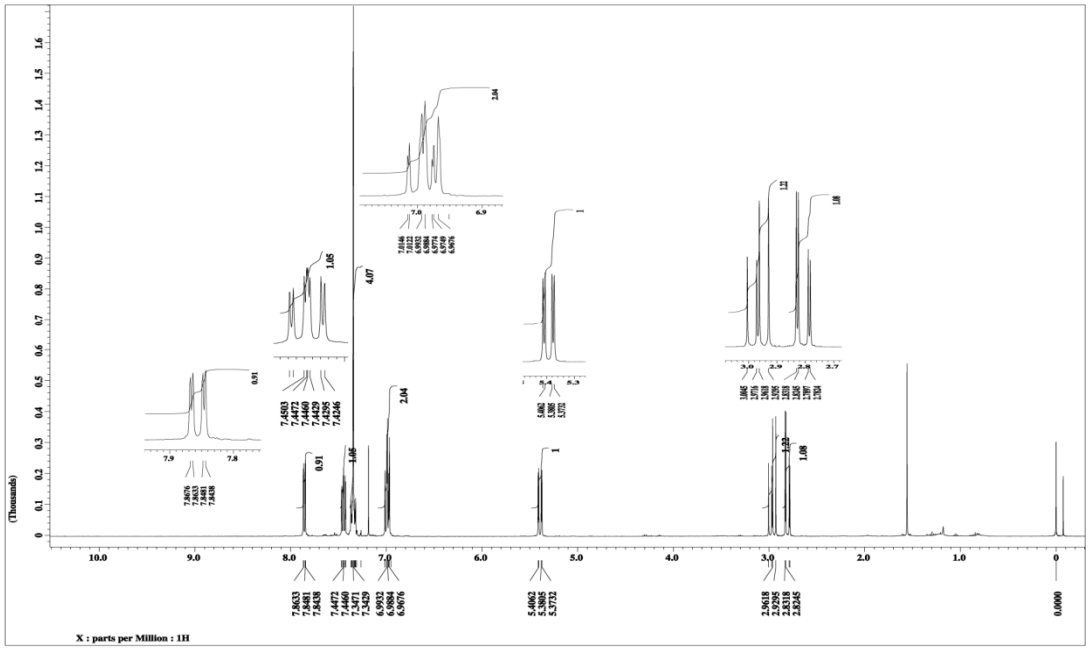


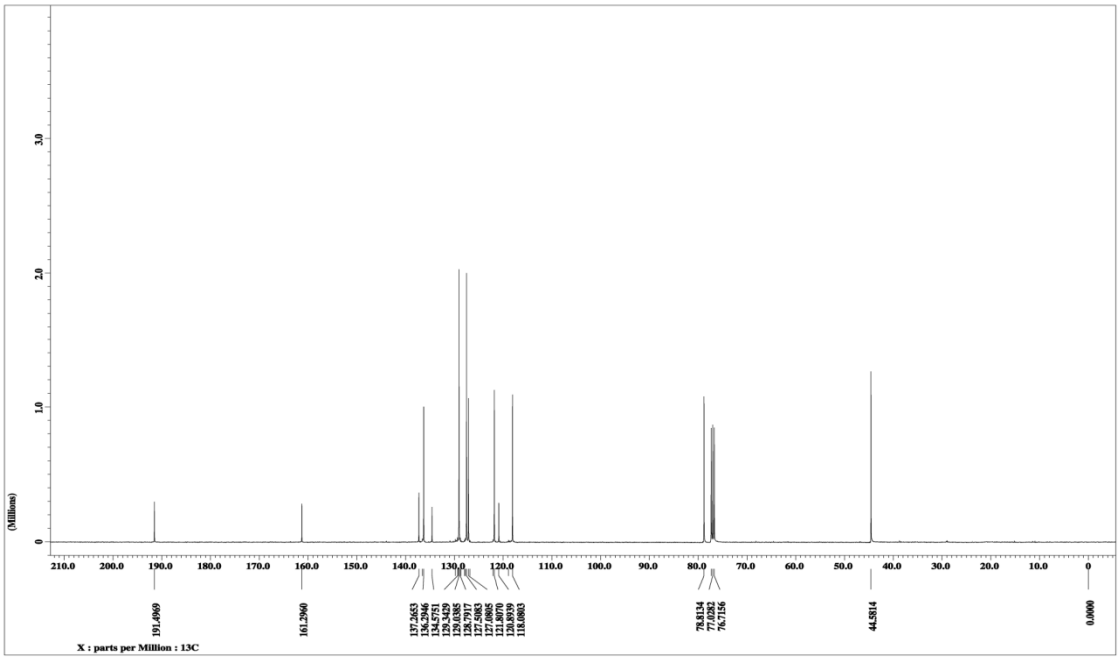




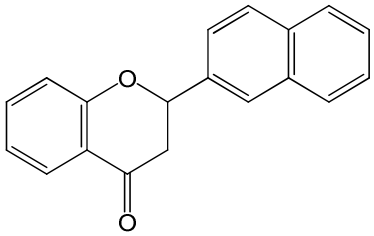
^{1}HNMR and ^{13}CNMR of 2- (4- clorophenyl) chroman-4-one MF7

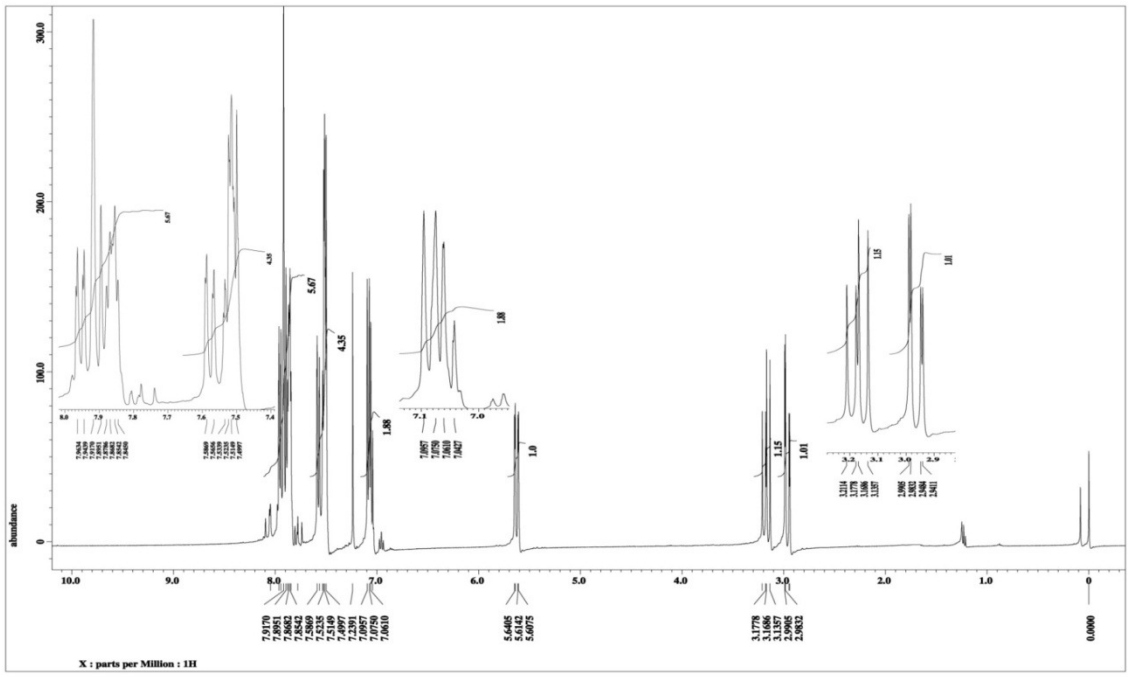


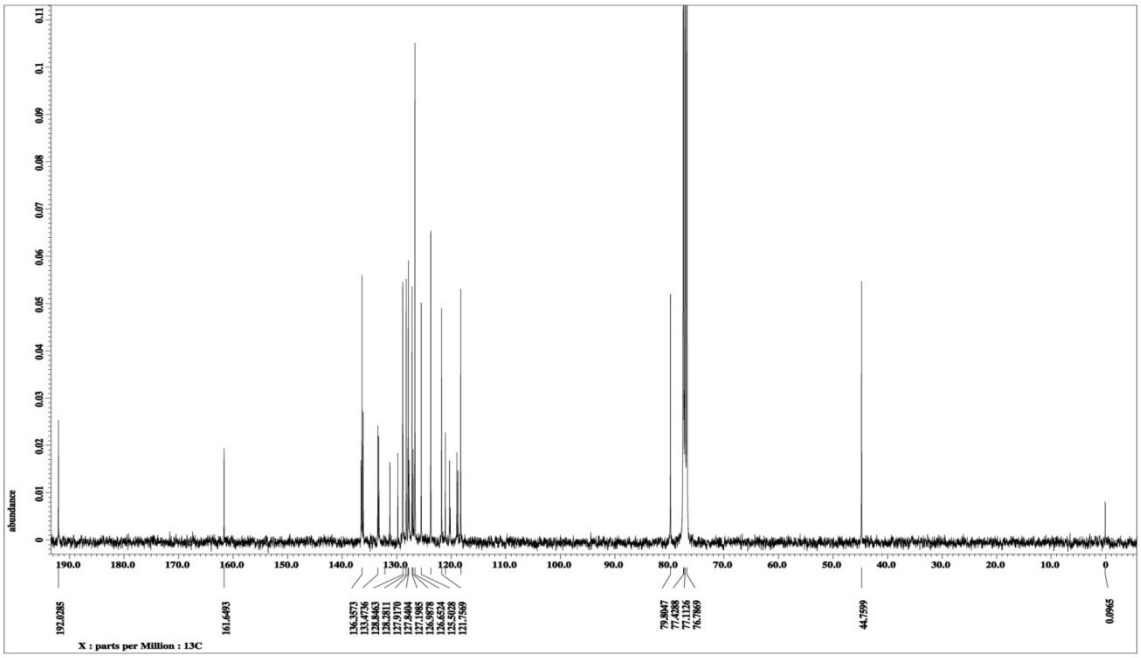




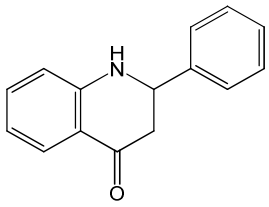
[1]HNMR and [13]CNMR of 2- (naphtalen-2-yl) chroman-4-one MF8

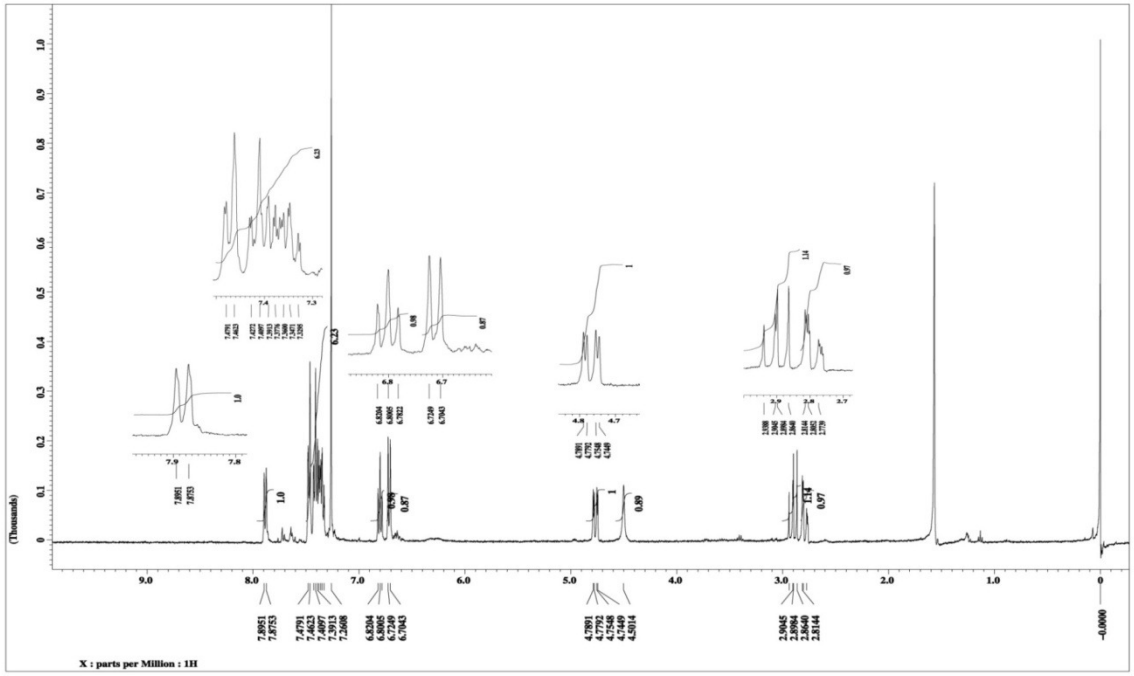


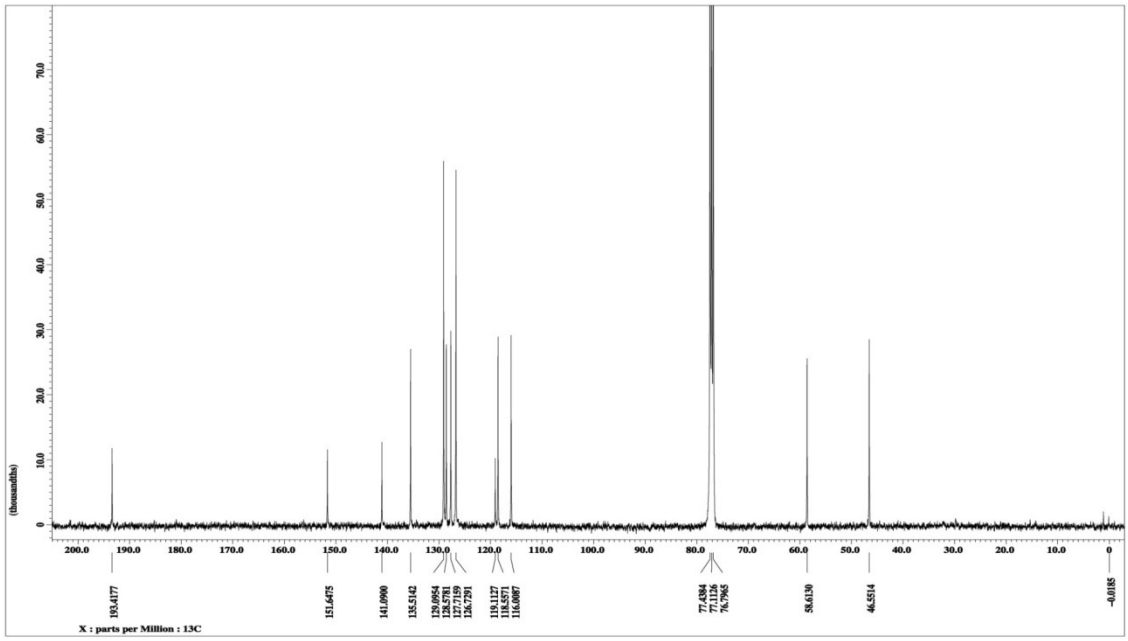




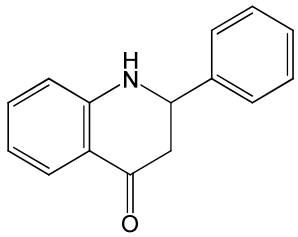
[1]HNMR and [13]CNMR of 2- phenyl-2, 3-dihydroquinolin-4-(1H)-one MF9

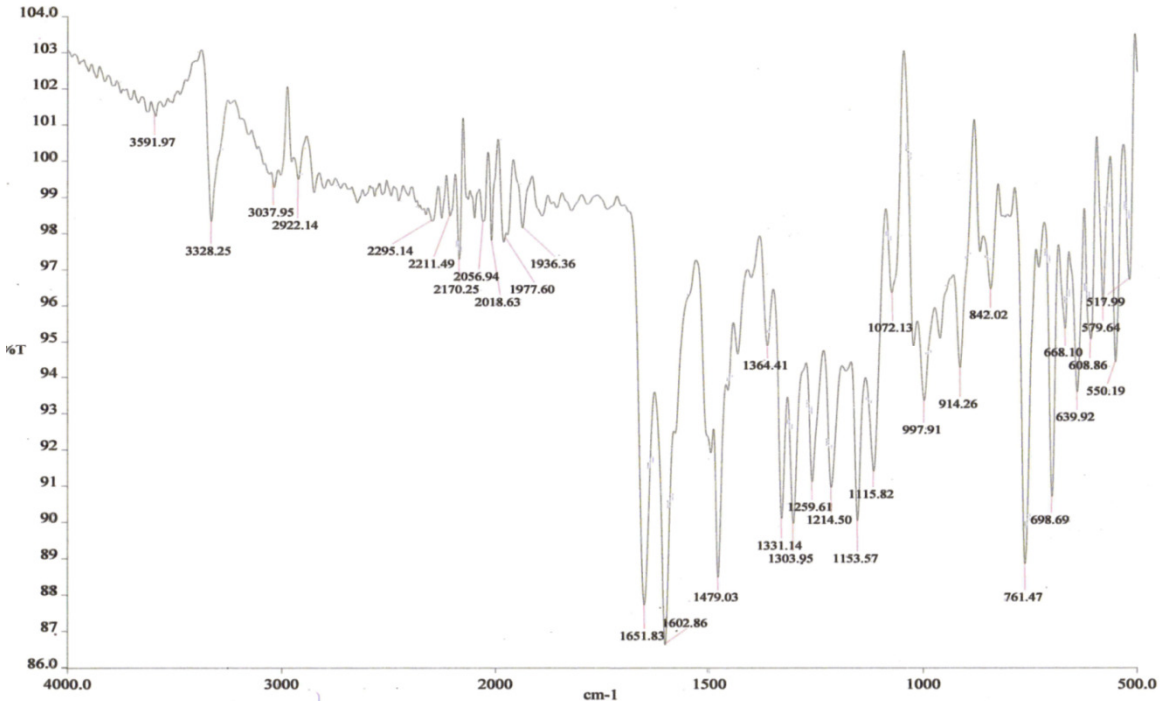




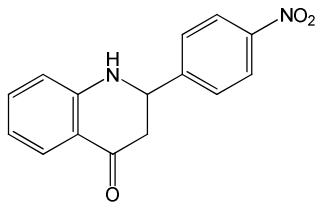


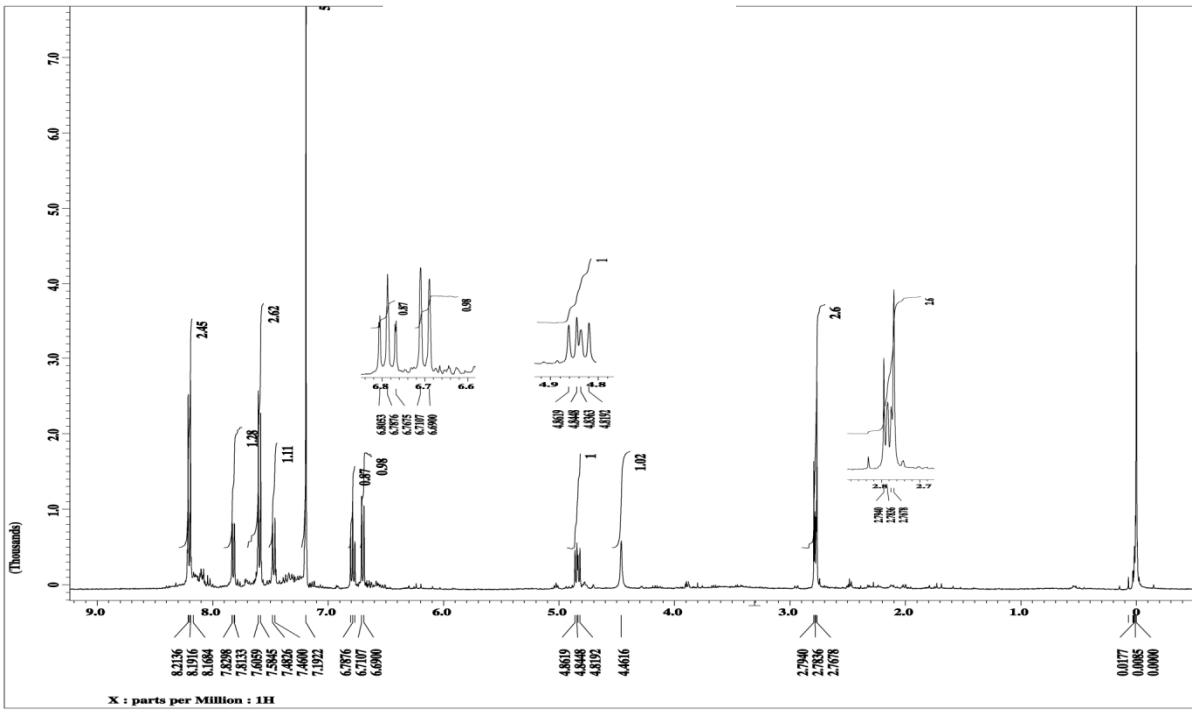
IR of 2- phenyl-2, 3-dihydroquinolin-4-(1H)-one MF9

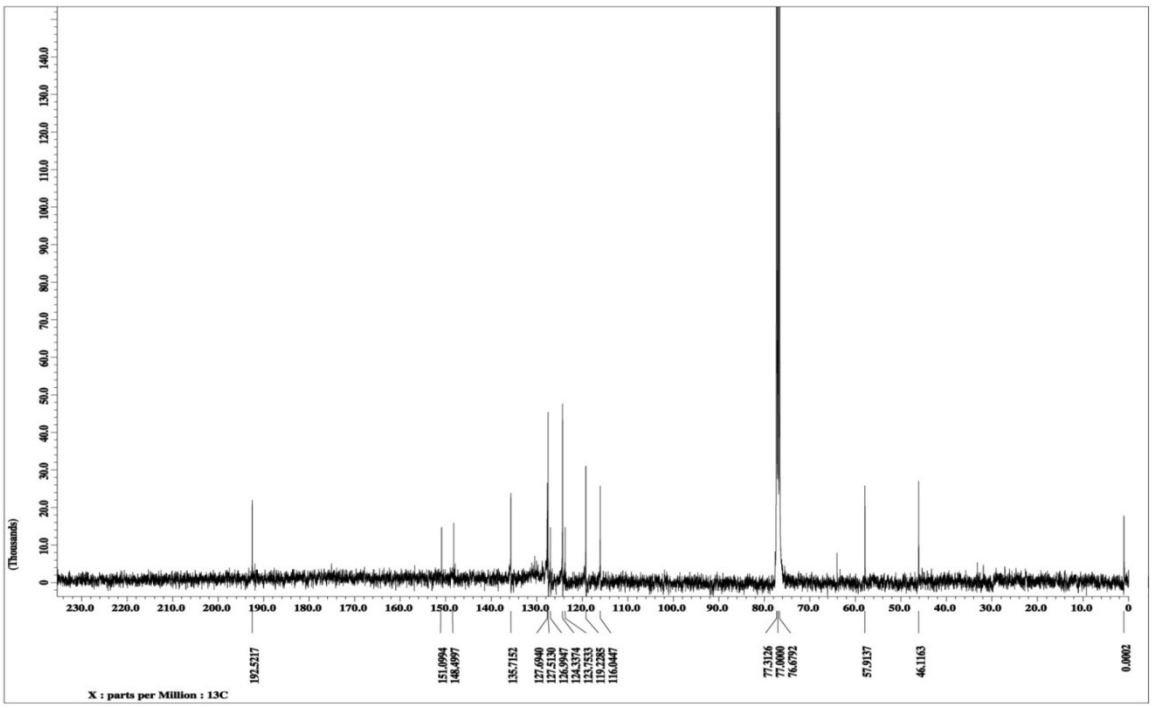




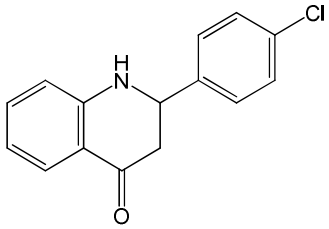
^{1}HNMR and ^{13}CNMR of 2- (4-nitrophenyl)-2, 3-dihydroquinolin-4-(1H)-one MF10

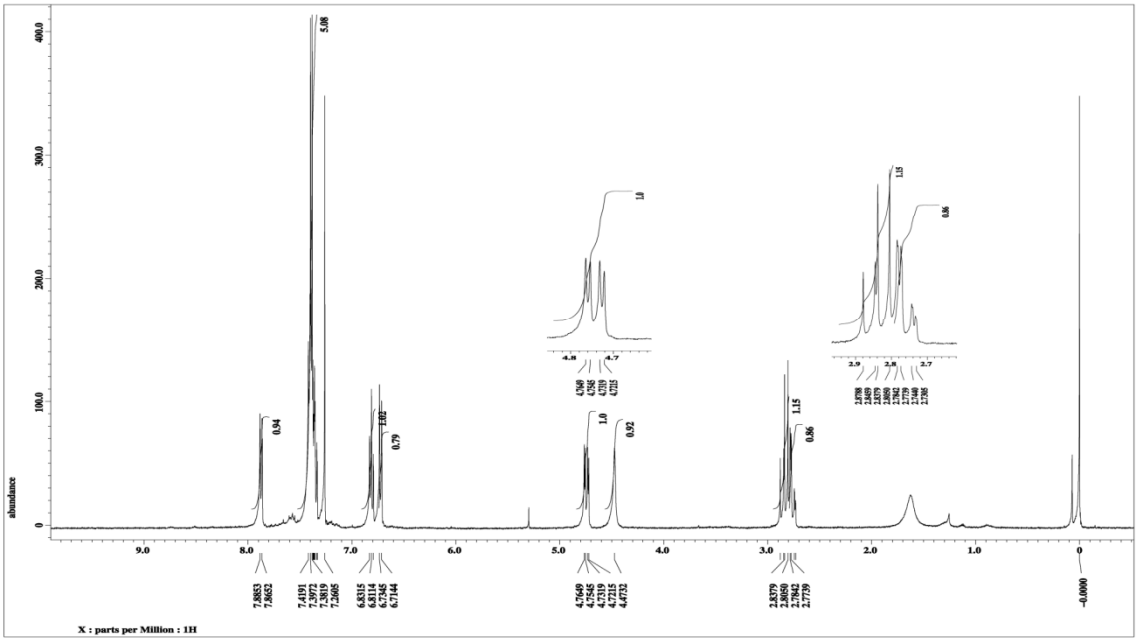


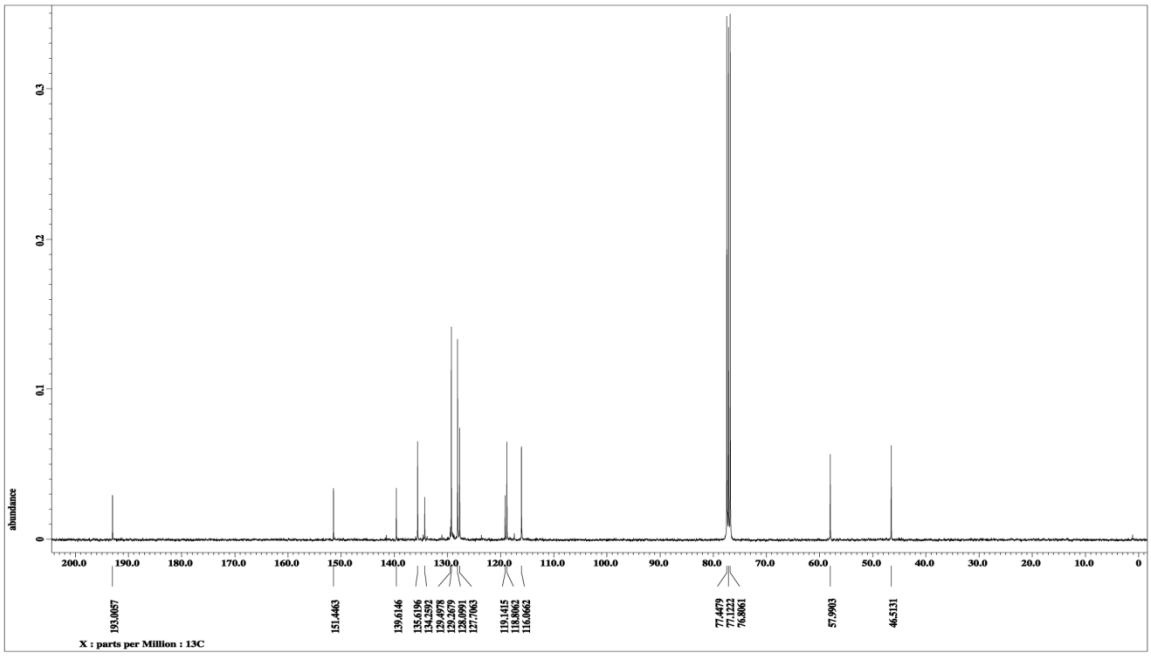




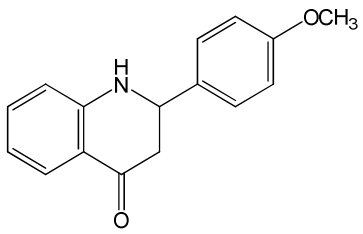
[1]HNMR and [13]CNMR of 2- (4-clorophenyl)-2, 3-dihydroquinolin-4-(1H)-one MF11

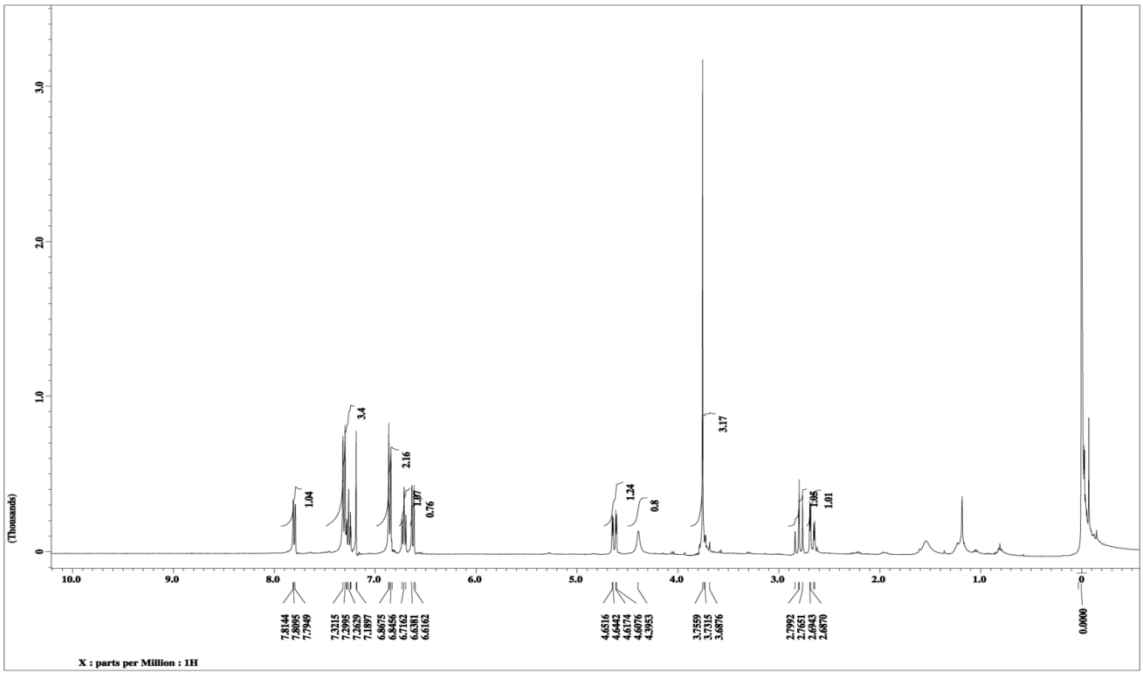


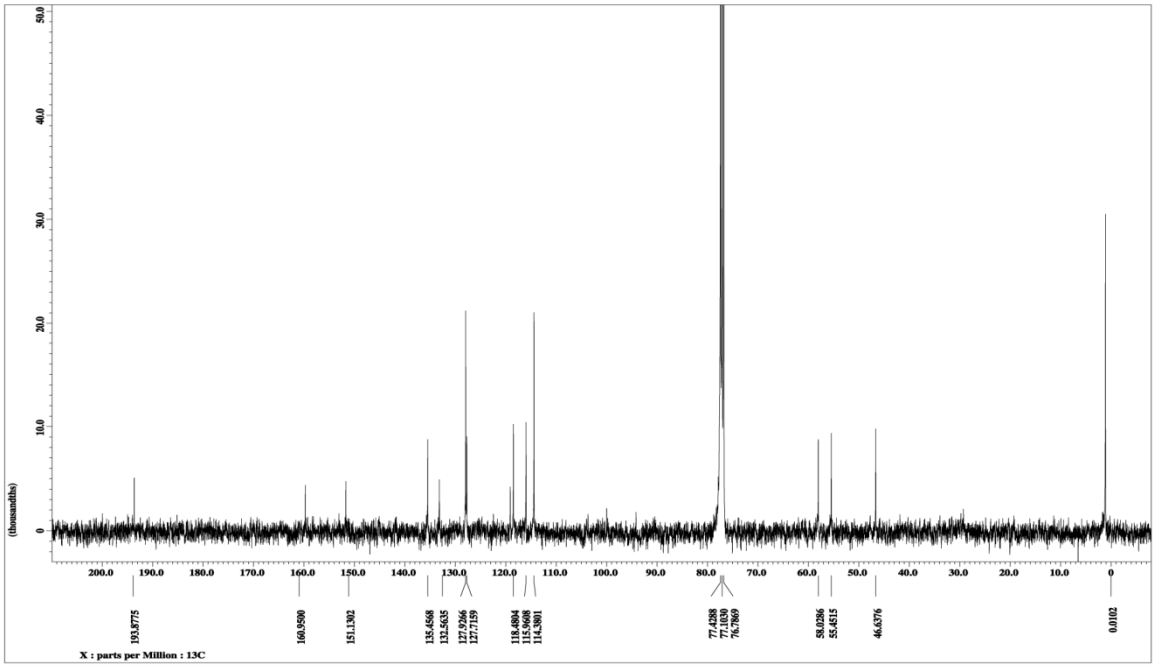




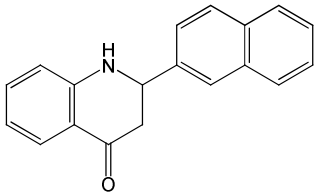
^{1}HNMR and ^{13}CNMR of 2- (4-methoxyphenyl)-2, 3-dihydroquinolin-4-(1H)-one MF12

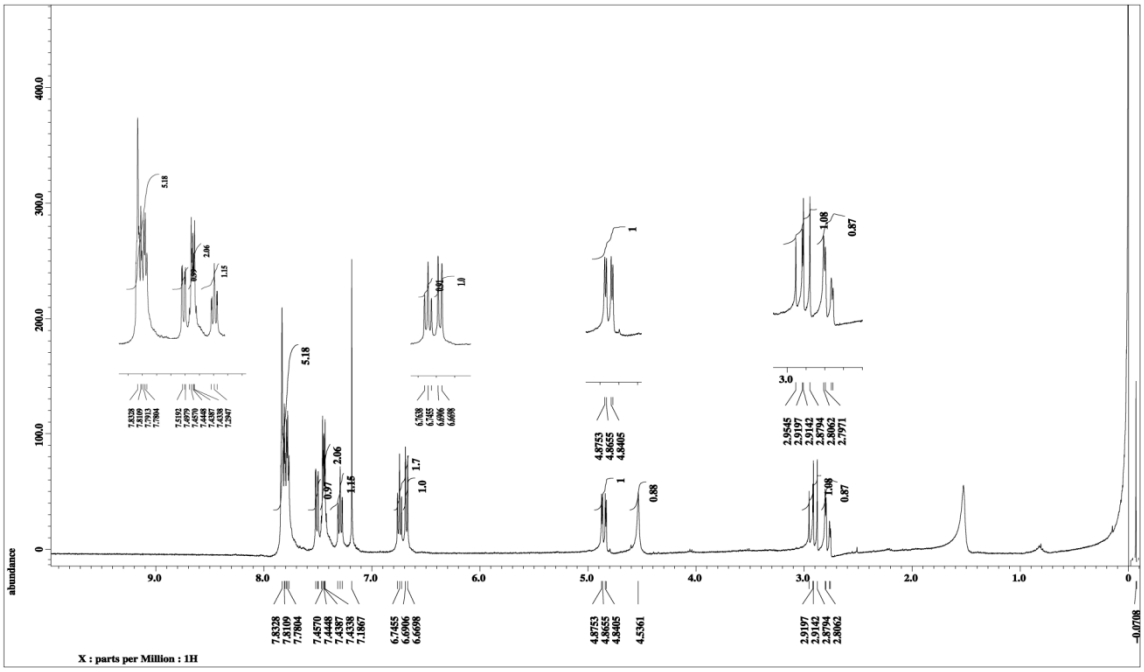


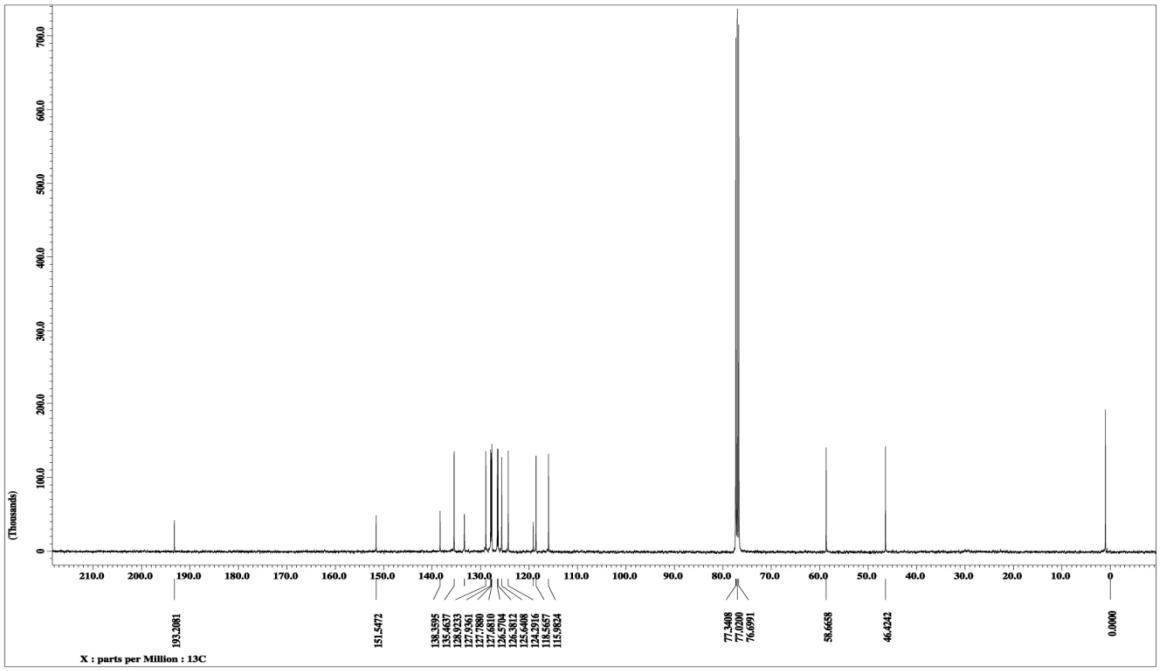




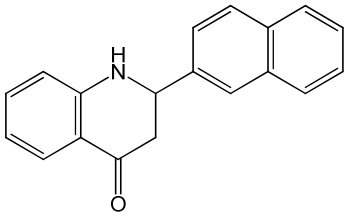
[1]HNMR and [13]CNMR of 2- (naphthalen2-yl)-2, 3-dihydroquinolin-4-(1H)-one MF13

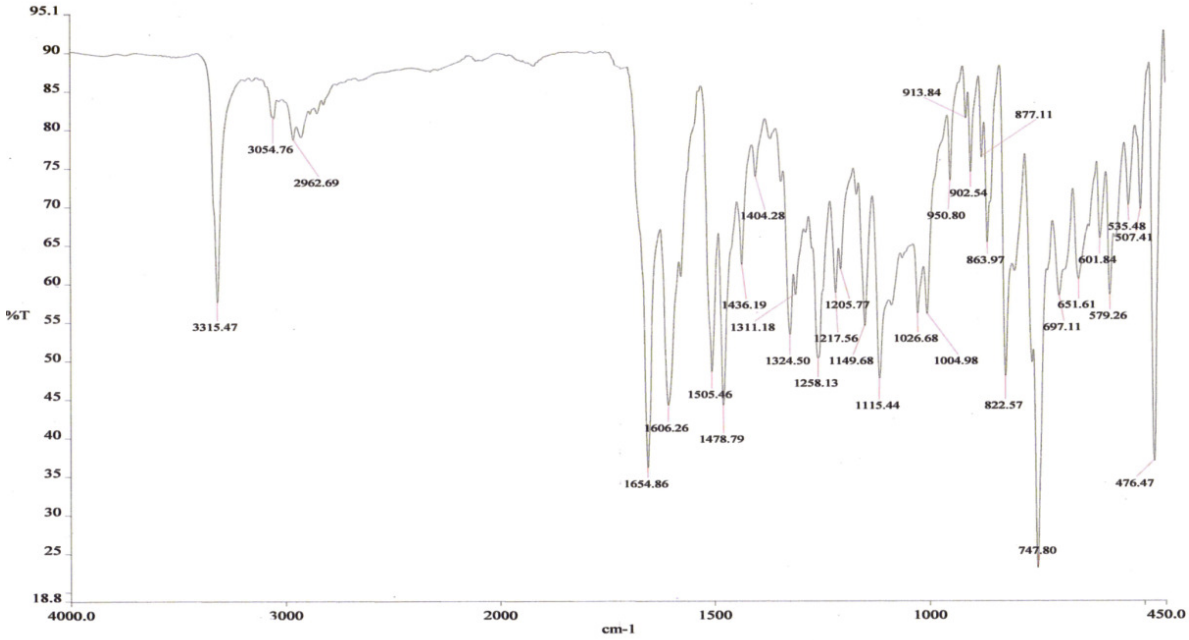




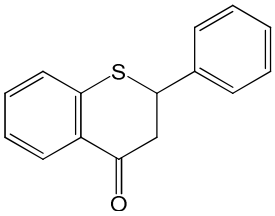


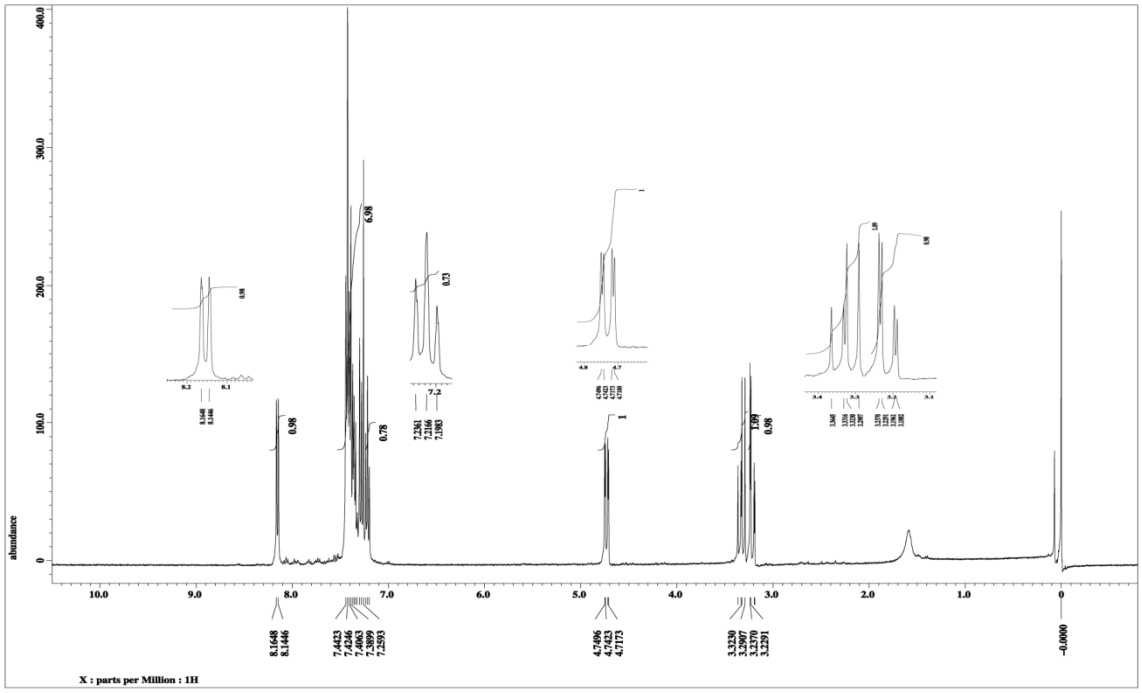
IR of 2- (naphthalen2-yl)-2, 3-dihydroquinolin-4-(1H)-one MF13

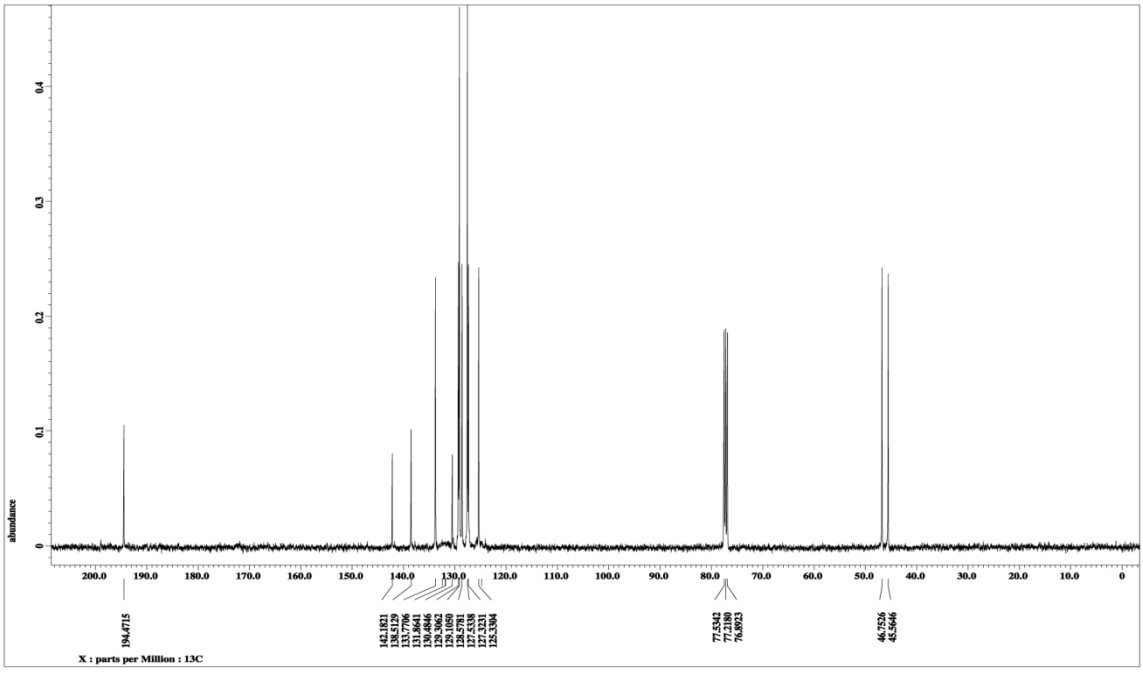




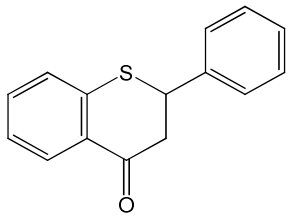
^{1}HNMR and ^{13}CNMR of 2-phenylthiochroman-4-one MF14

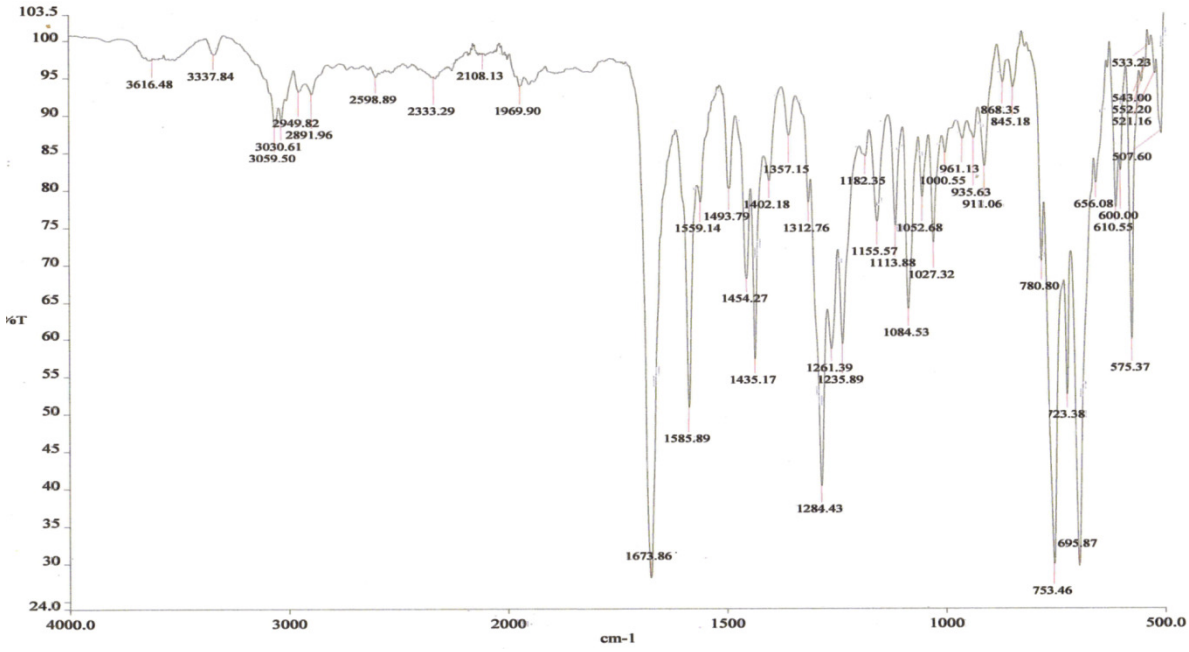




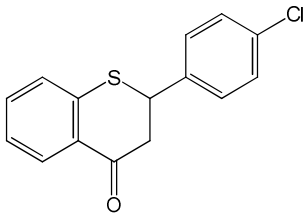


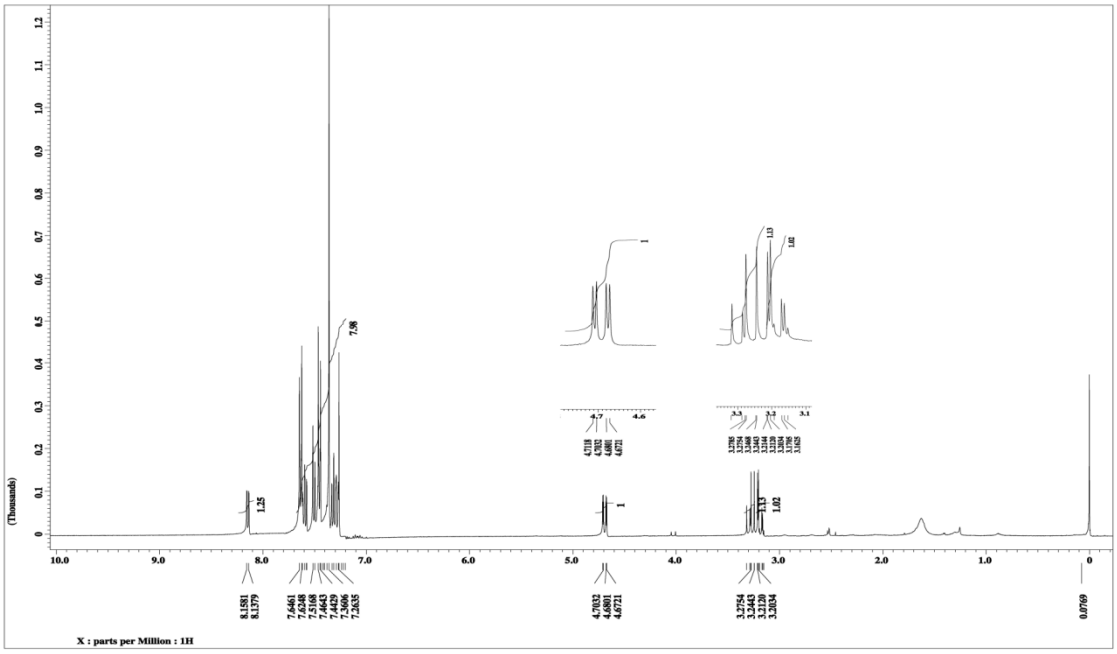
IR of 2-phenylthiochroman-4-one MF14

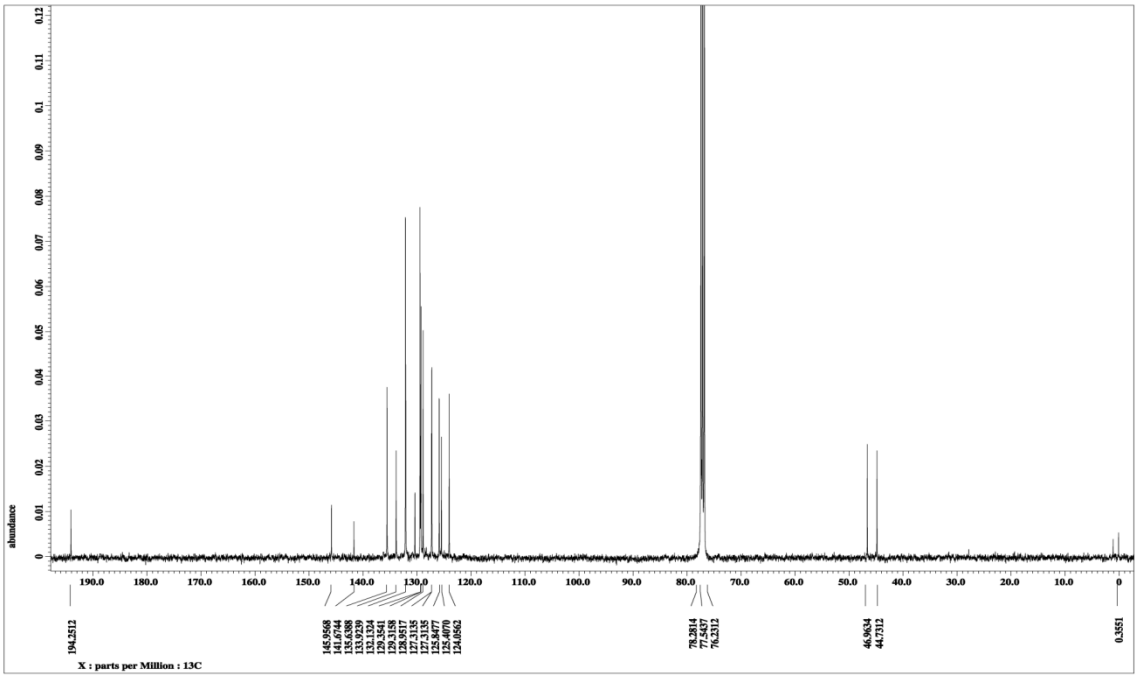




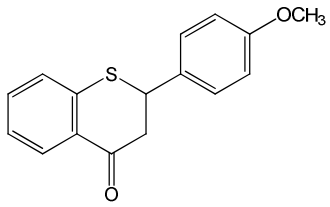
^{1}HNMR and ^{13}CNMR of 2-(4-clorophenyl) thiochroman-4-one MF15

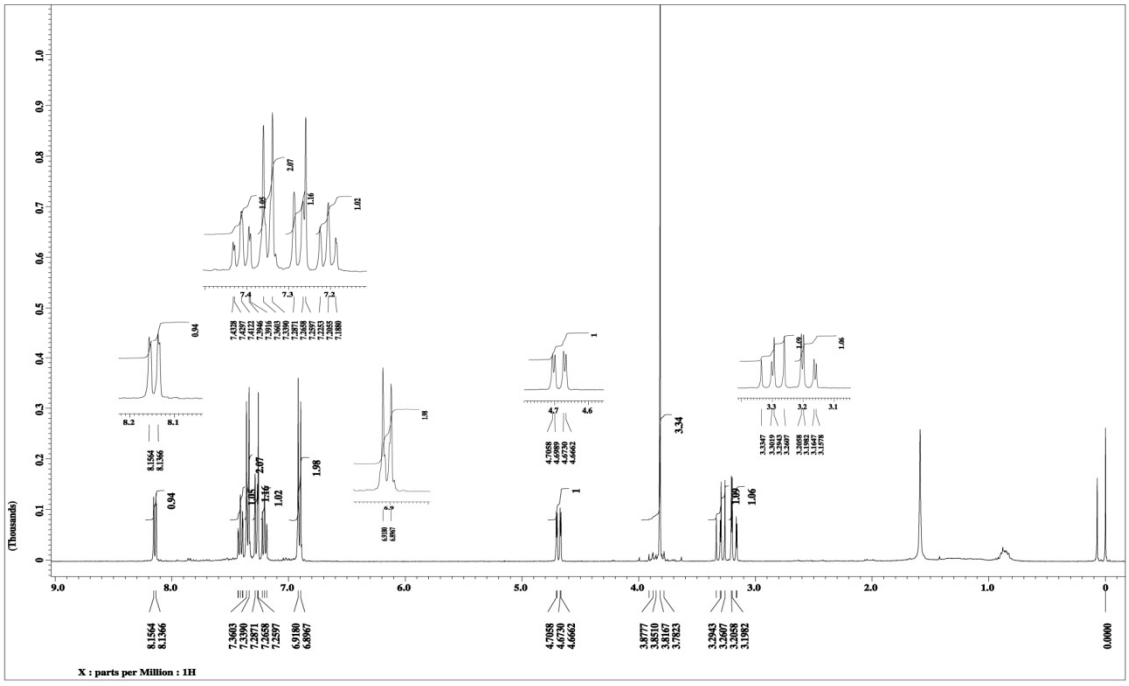


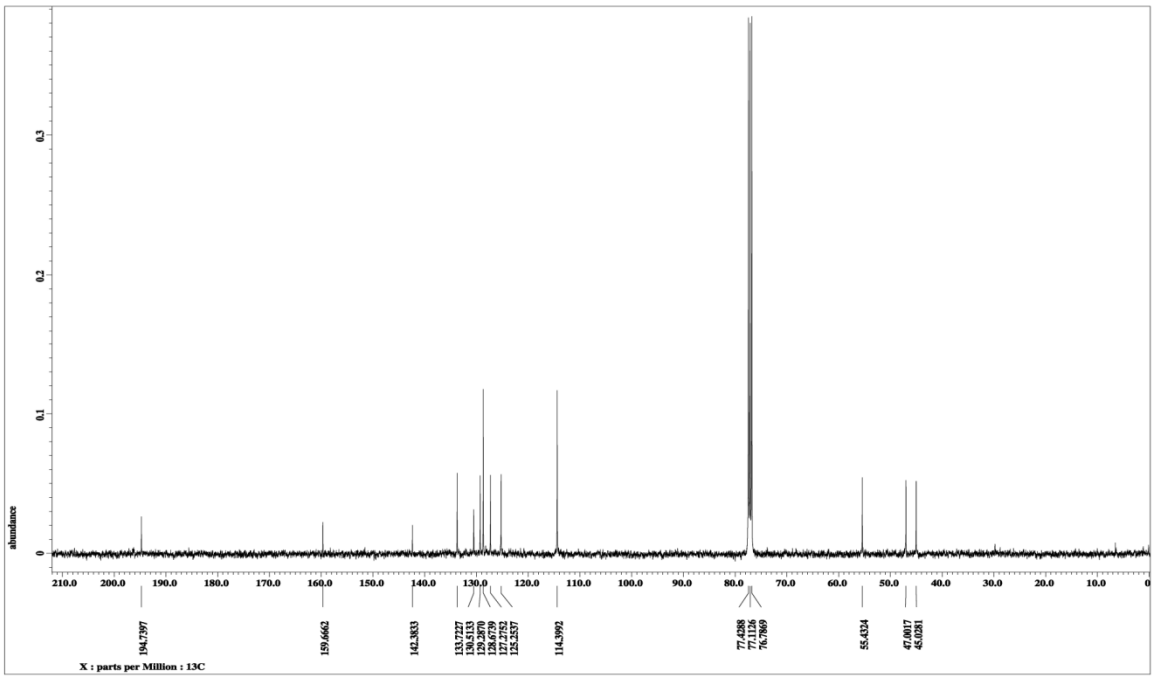




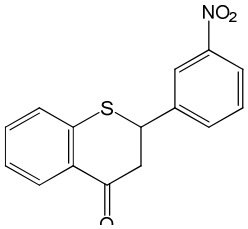
[1]HNMR and [13]CNMR of 2-(4-methoxyphenyl) thiochroman-4-one MF16

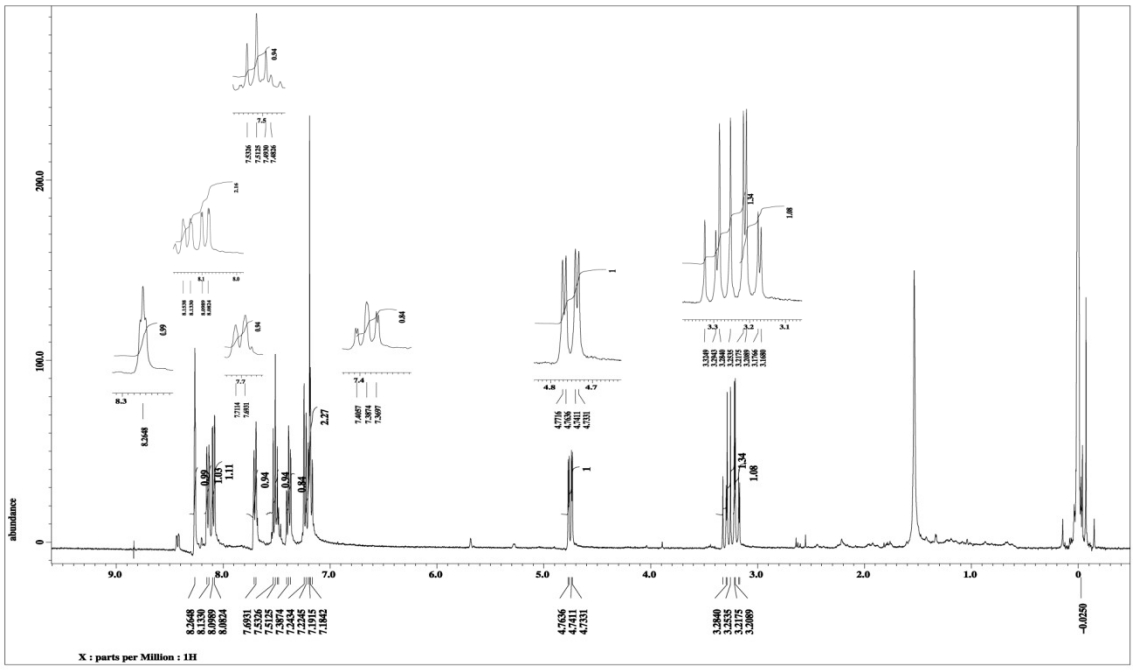


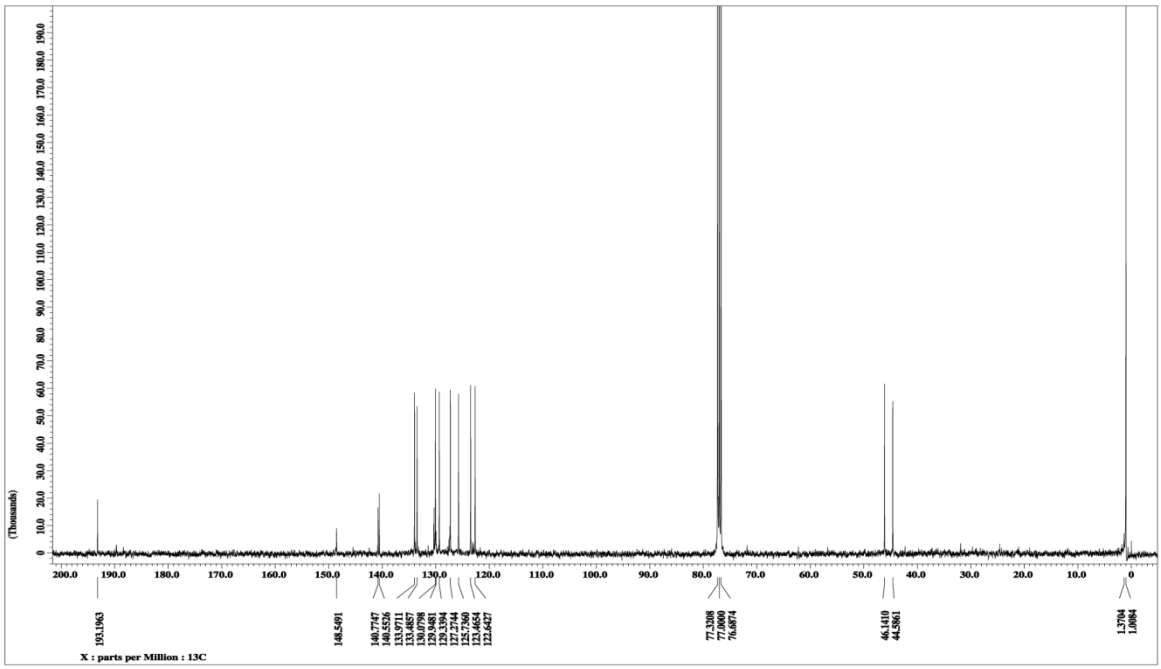




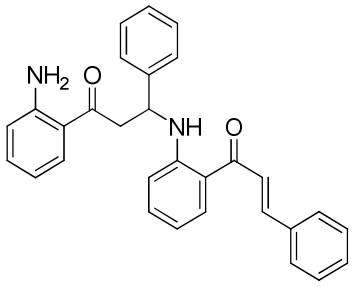
^{1}HNMR and ^{13}CNMR of 2-(3-nitrophenyl) thiochroman-4-one MF17

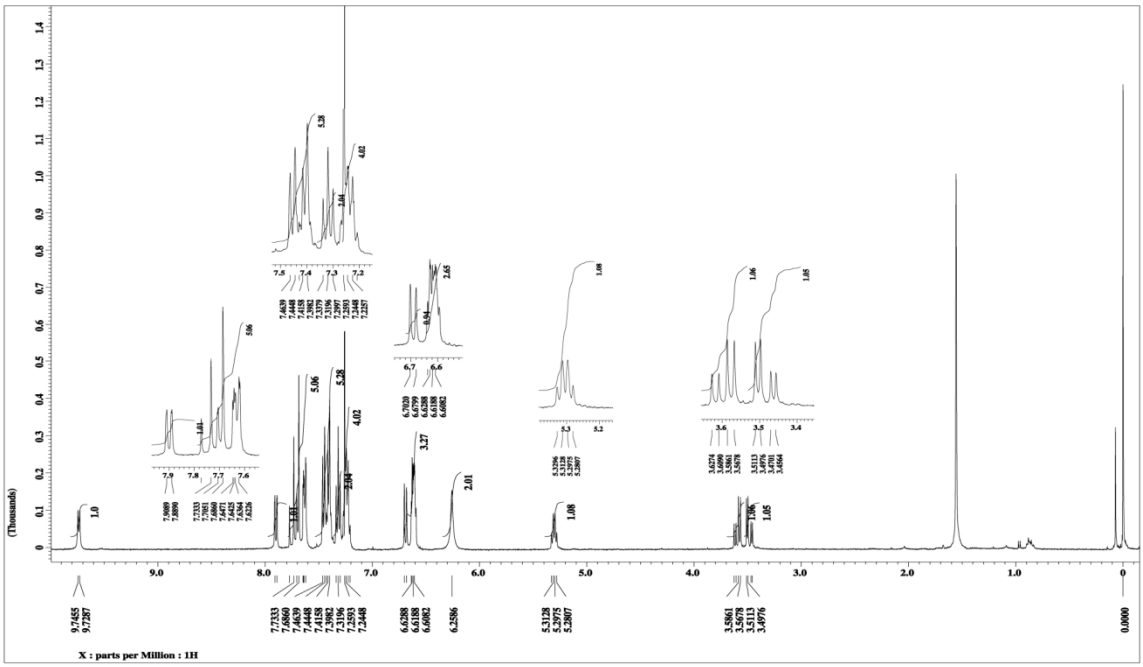


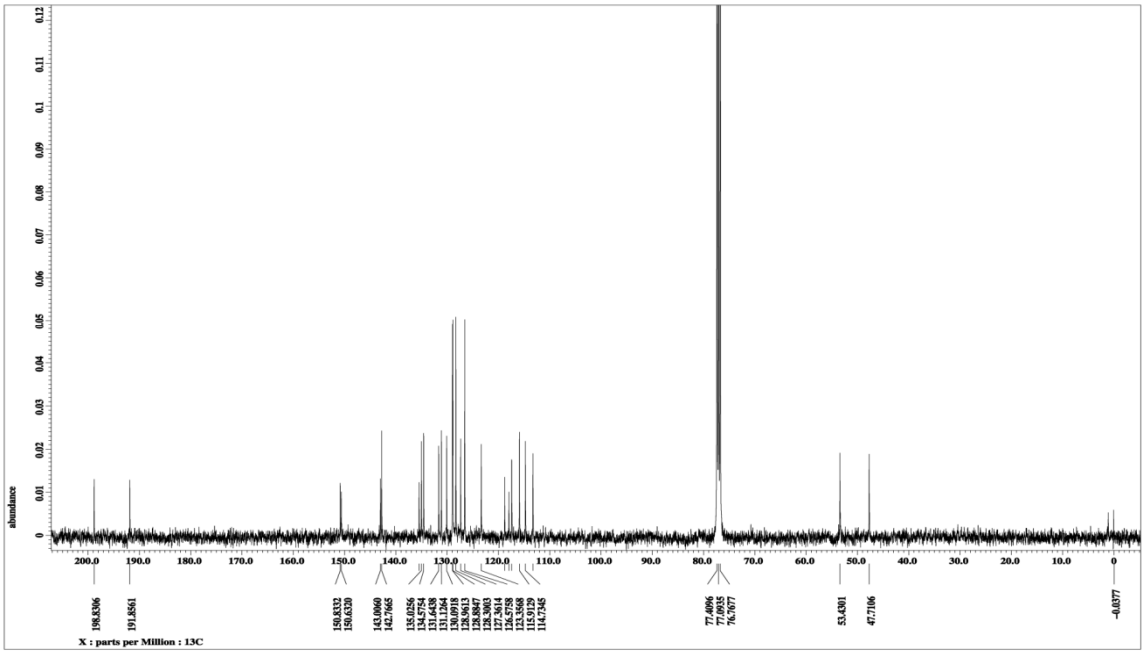




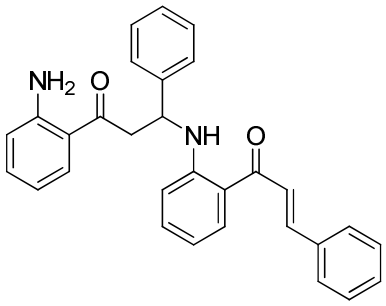
^{1}HNMR and ^{13}CNMR of (E)-1-(2-(3-(2-aminophenyl)-3-oxo-1-phenylpropylamino) phenyl)-3-phenylprop-2-en-1-one MFs

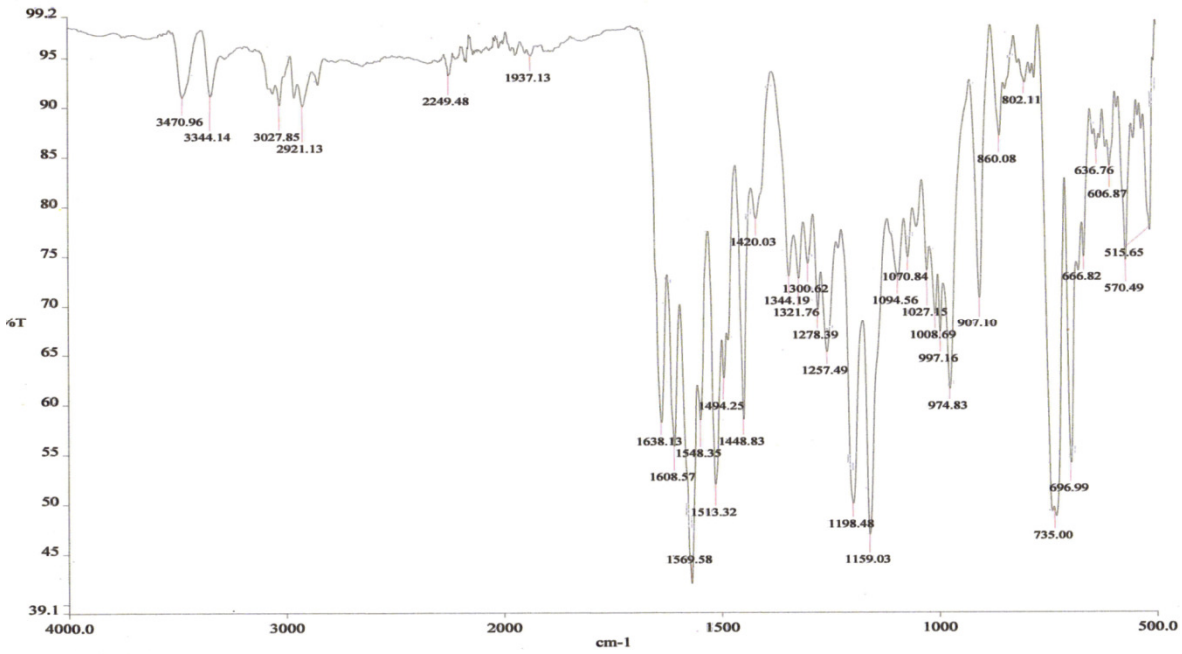






IR of (E)-1-(2-(3-(2-aminophenyl)-3-oxo-1-phenylpropylamino) phenyl)-3 -phenylprop-2-en-1-one; MFs

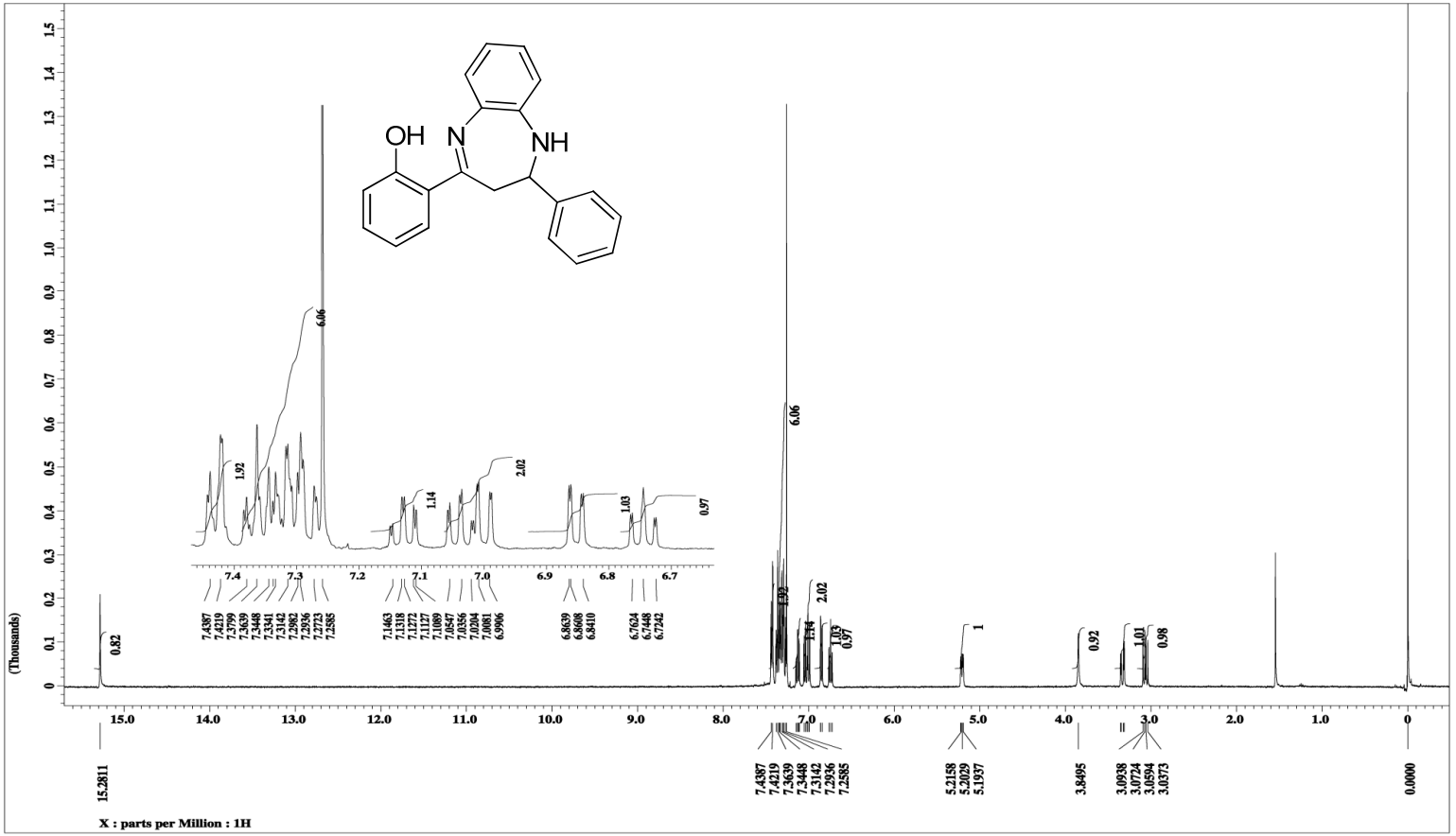




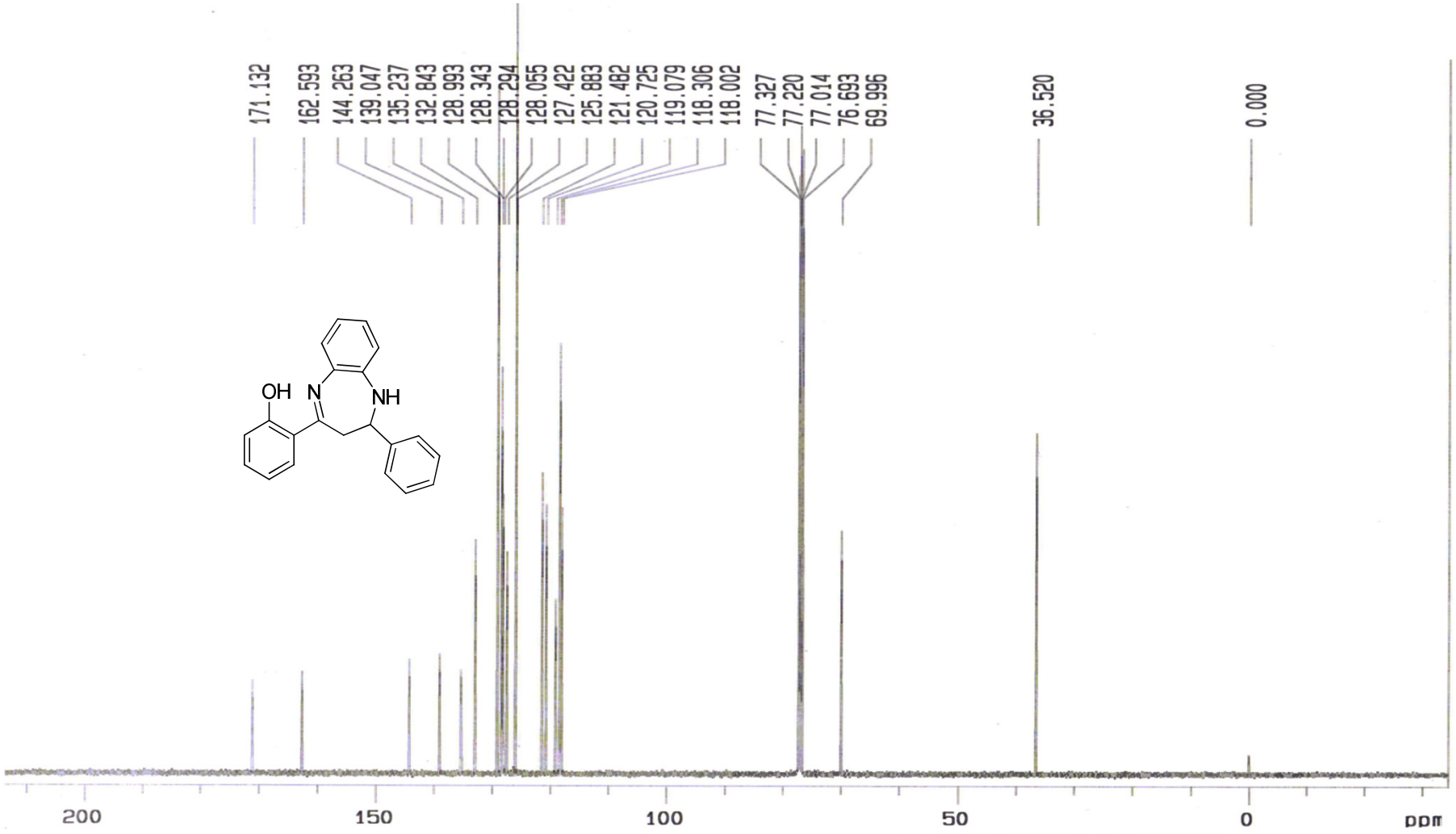
APPENDIX B

SUPPLEMENTARY DATA OF CHAPTER 8 AND 9

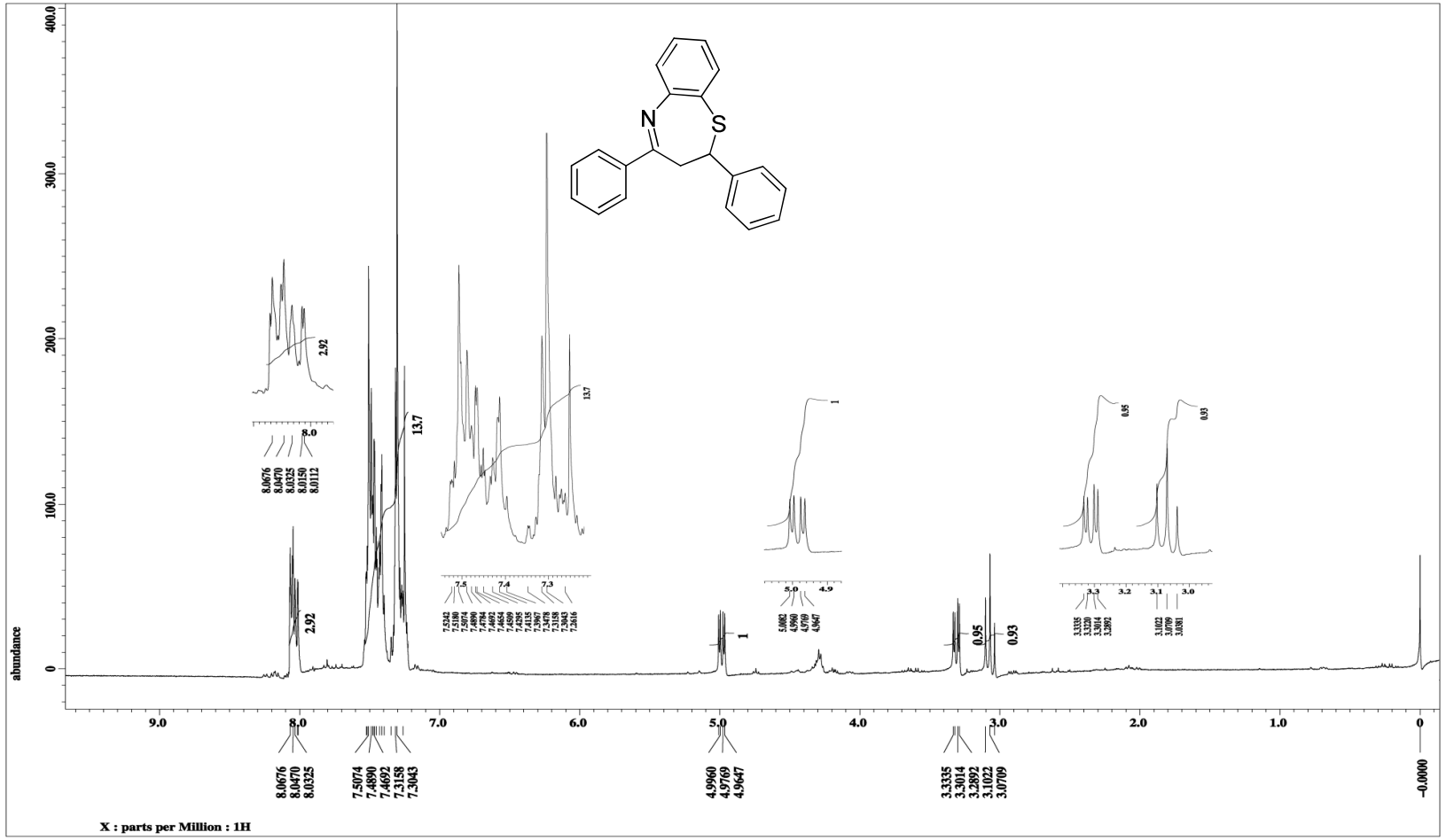
[1]HNMR of 2-(2-phenyl-2, 3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)phenol MAZ



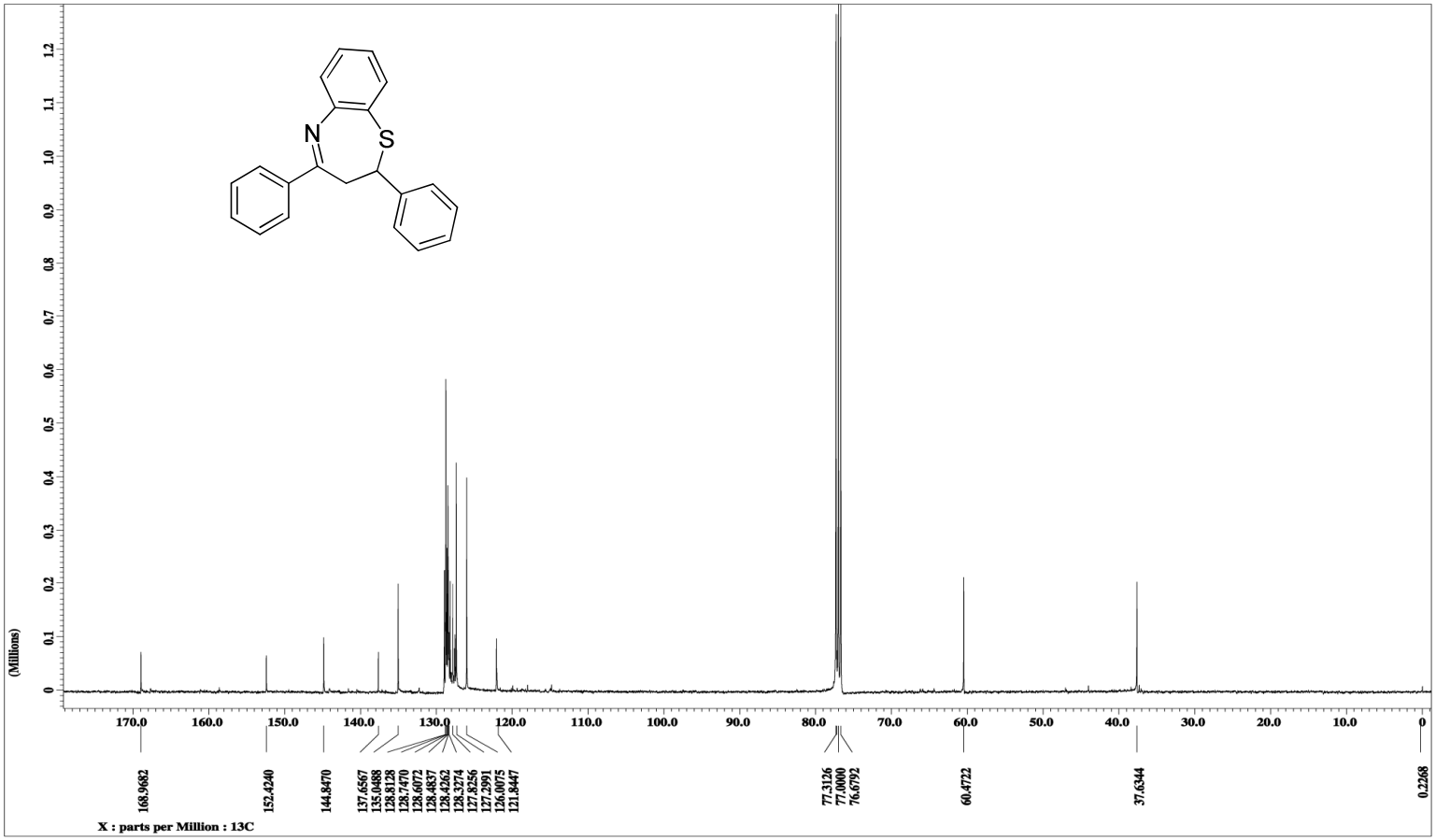
^{13}CNMR of 2-(2-phenyl-2, 3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)phenol MAZ



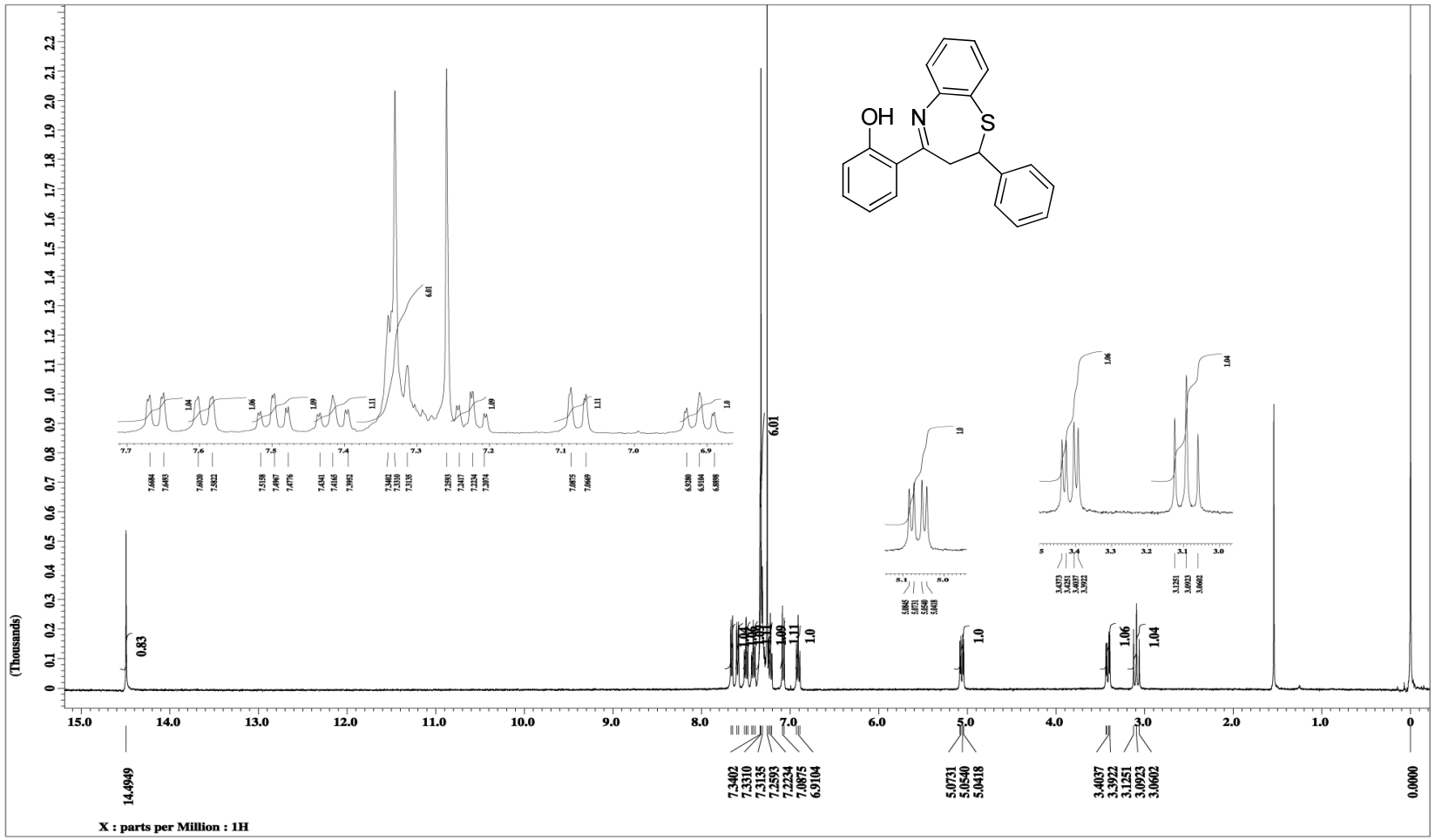
[1]HNMR of 2, 4-diphenyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA1



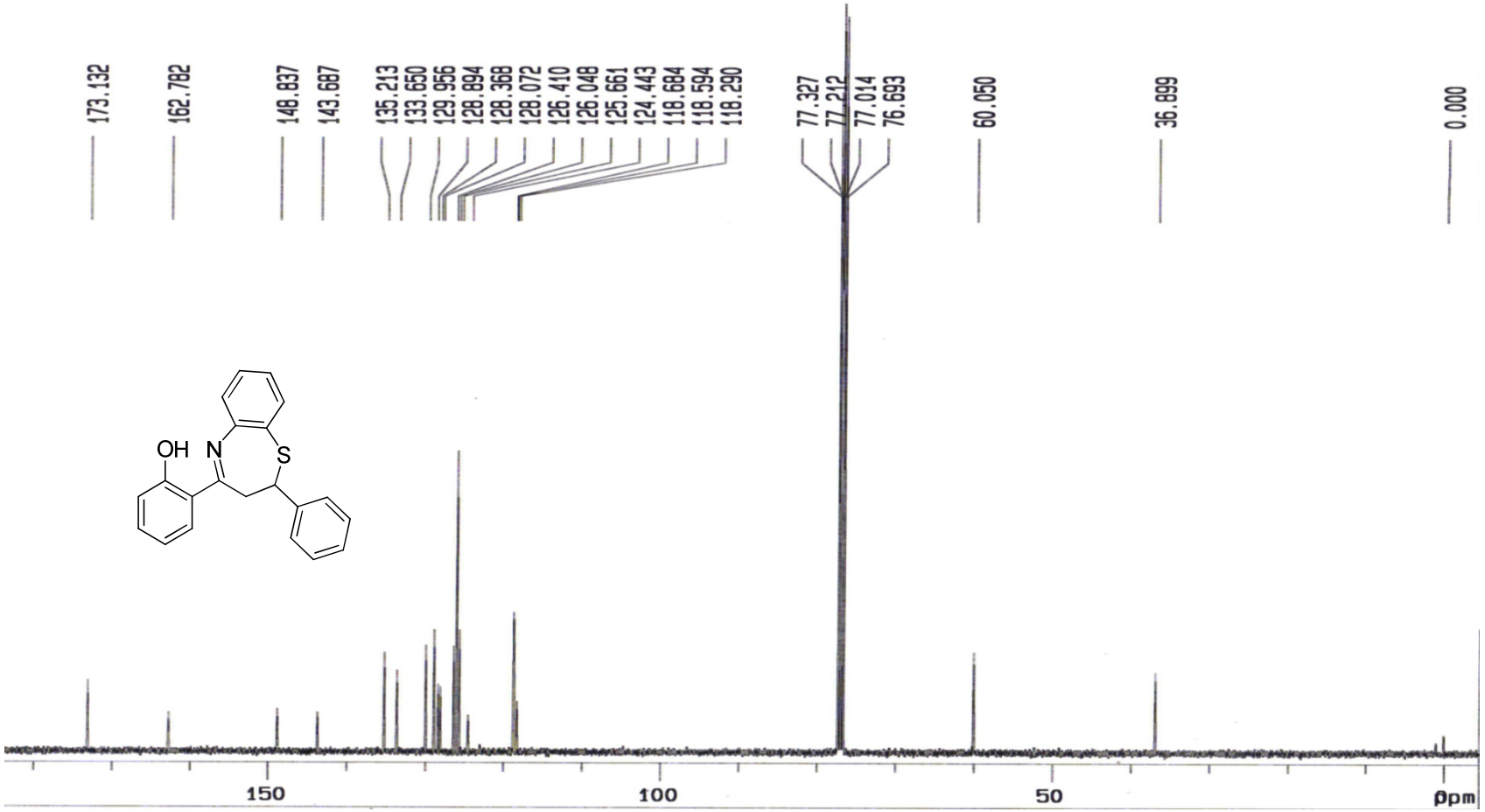
^{13}CNMR of 2, 4-diphenyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA1



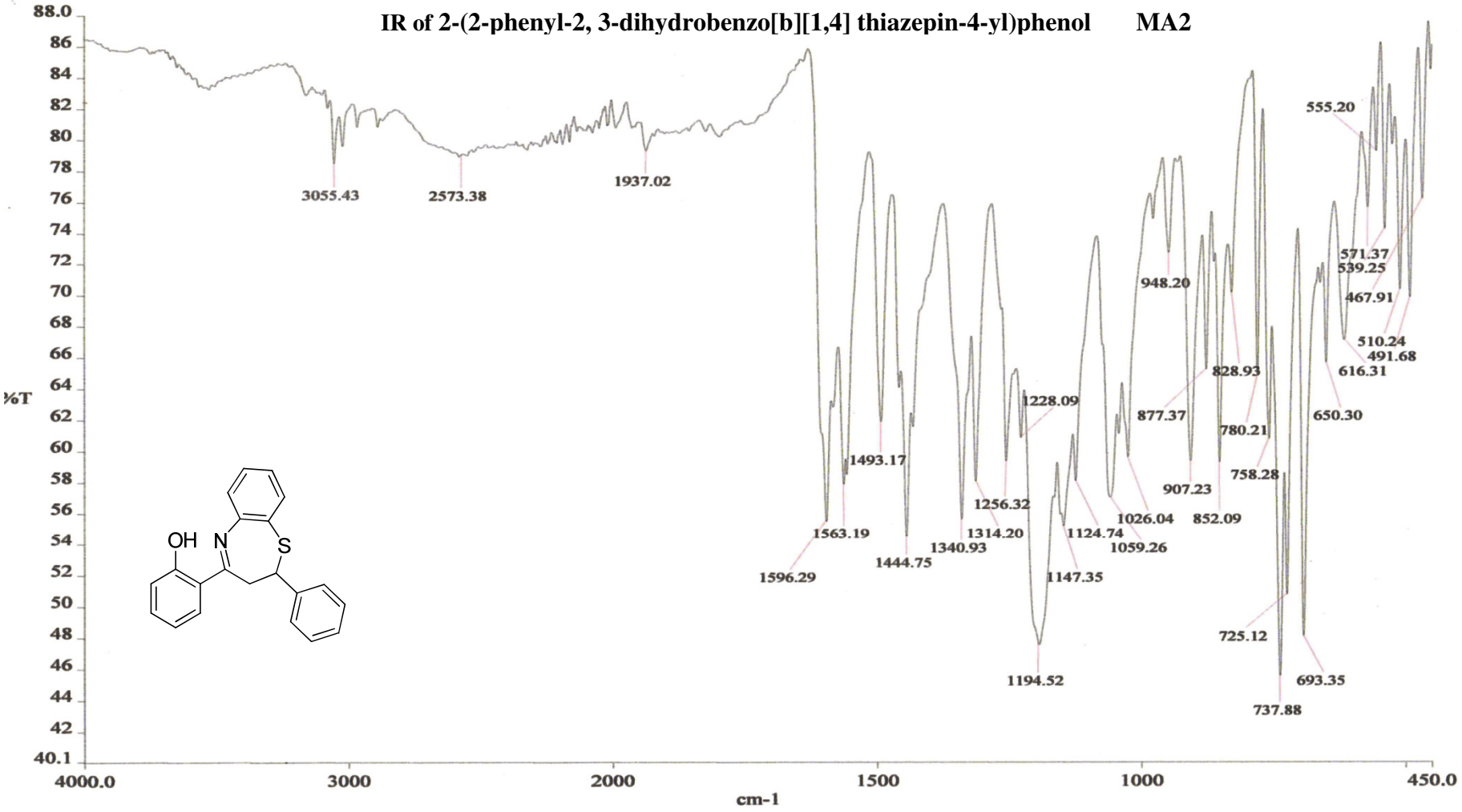
[1]HNMR of 2-(2-phenyl-2, 3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol MA2



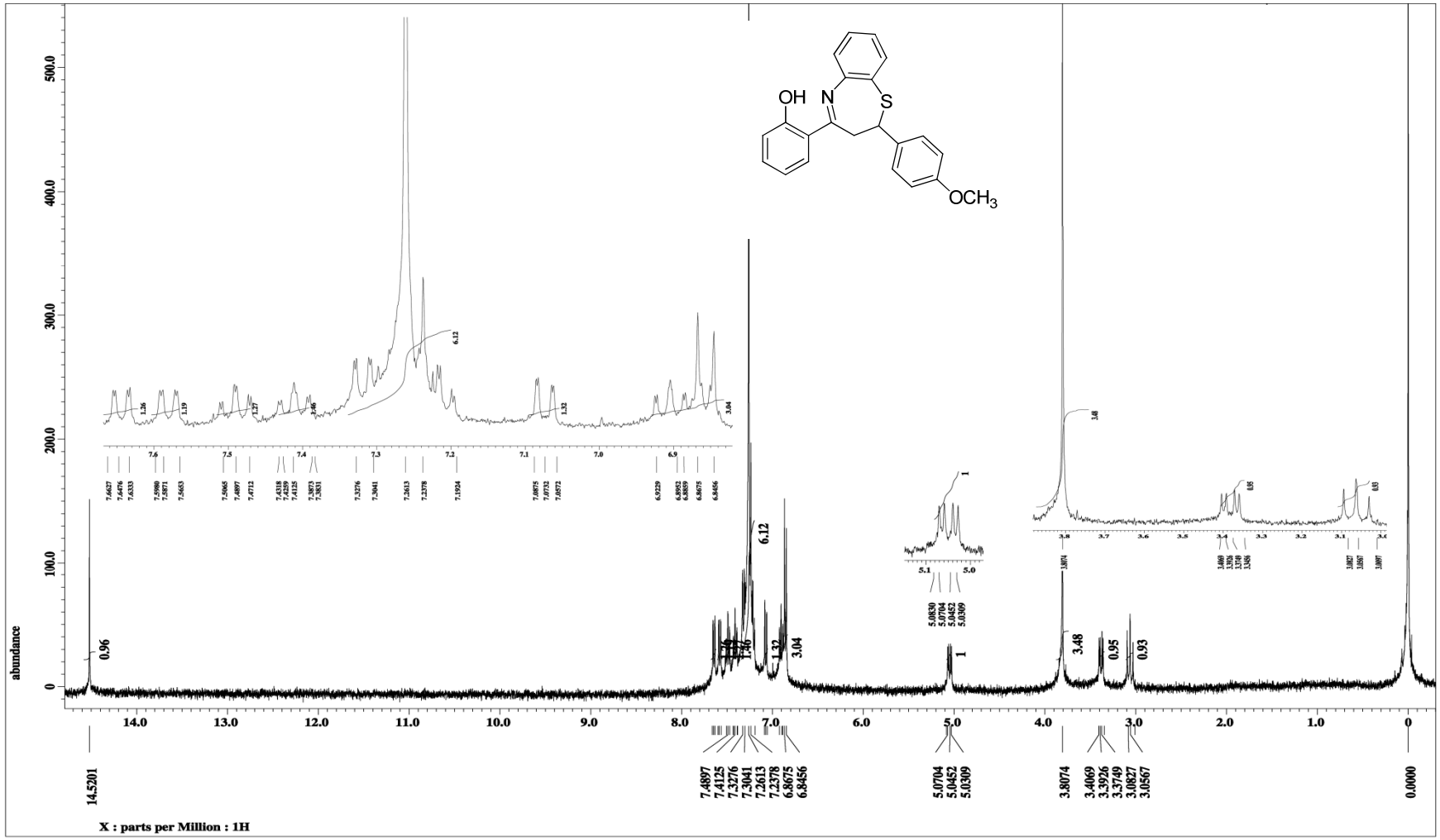
^{13}CNMR of 2-(2-phenyl-2, 3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol MA2



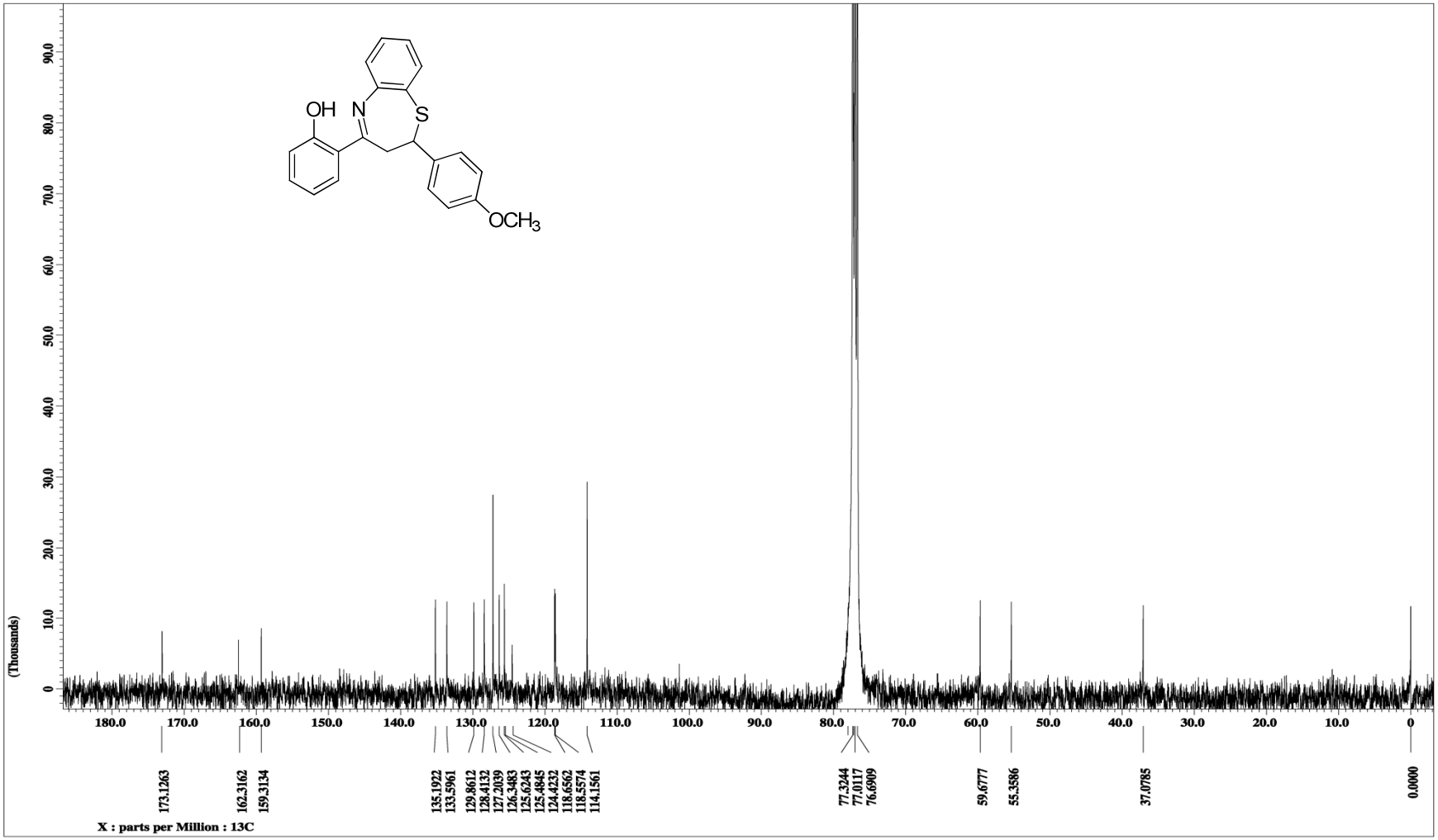
IR of 2-(2-phenyl-2, 3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenol MA2



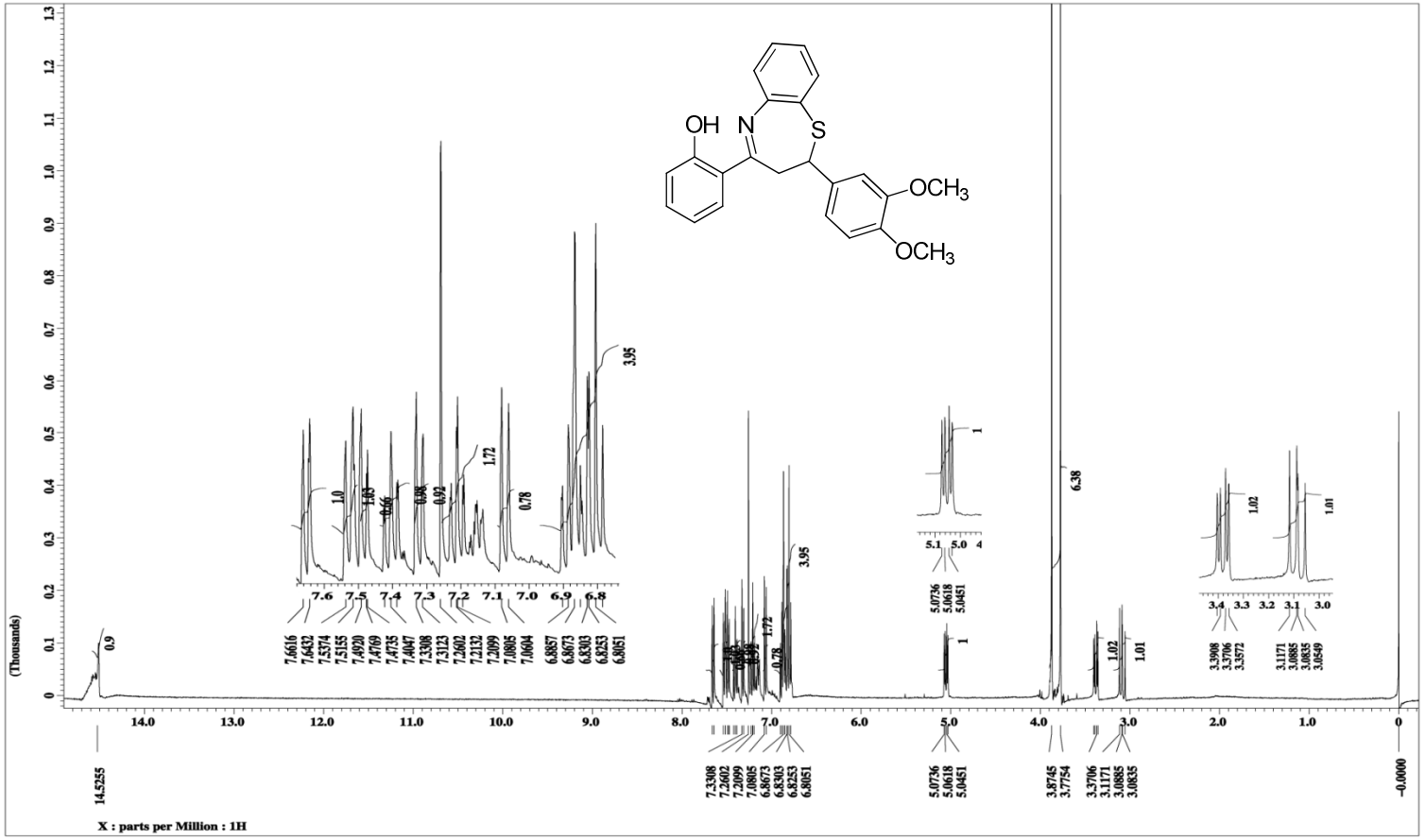
[1]HNMR of 2-(2-(4-methoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA3



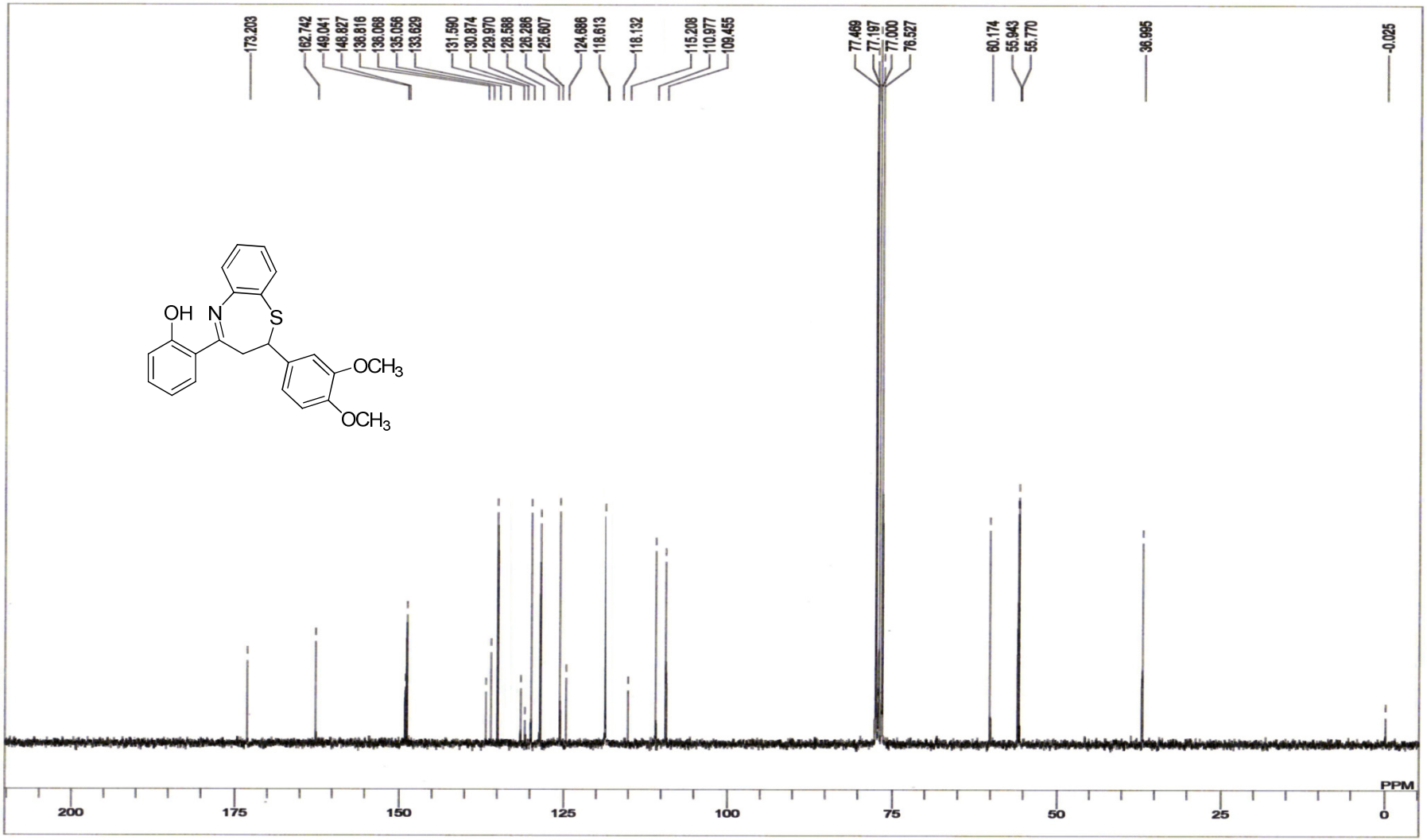
^{13}CNMR of 2-(2-(4-methoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA3



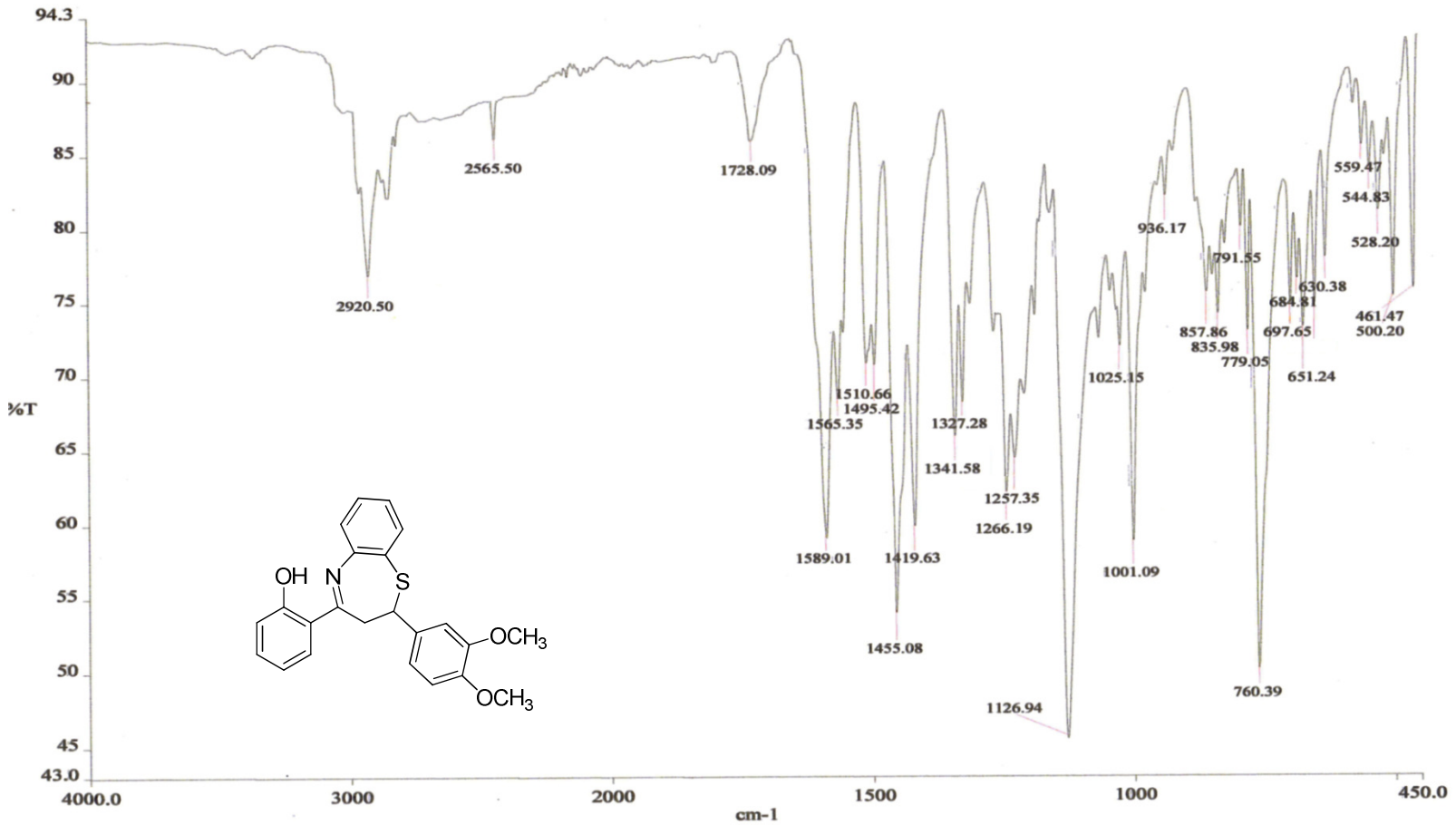
[1]HNMR of 2-(2-(3, 4-dimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA4



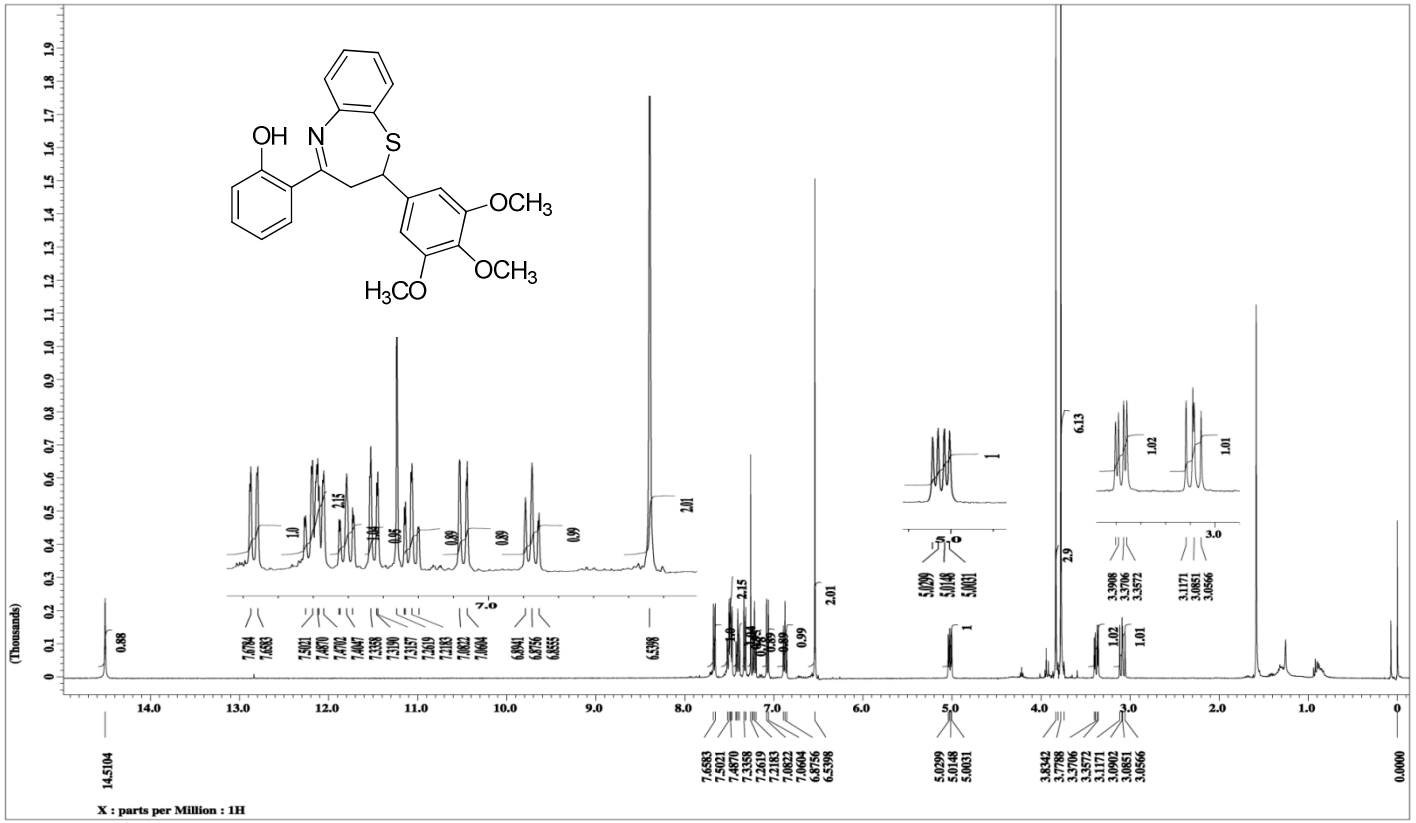
^{13}CNMR of 2-(2-(3, 4-dimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA4



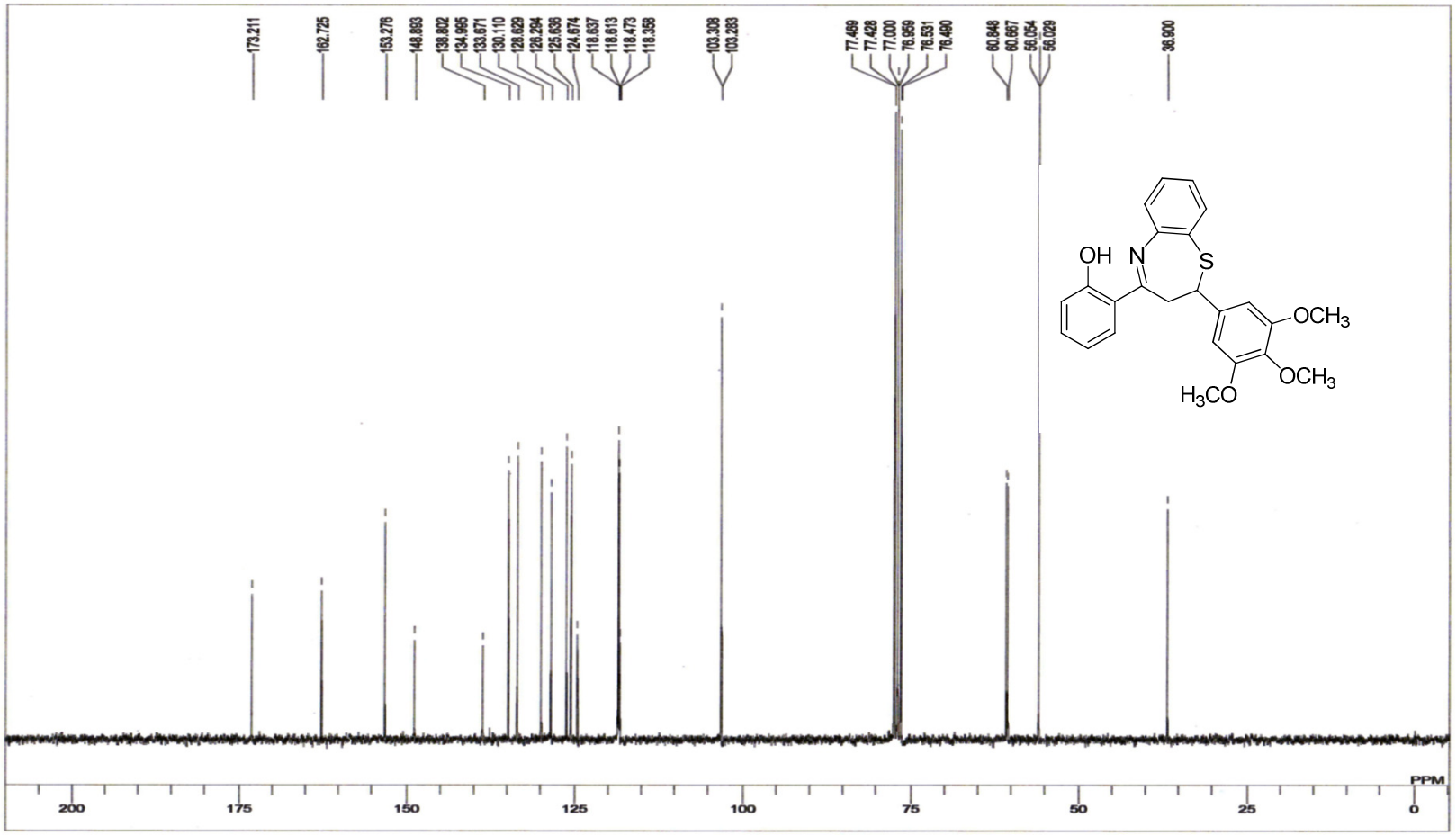
IR of 2-(2-(3, 4-dimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA4



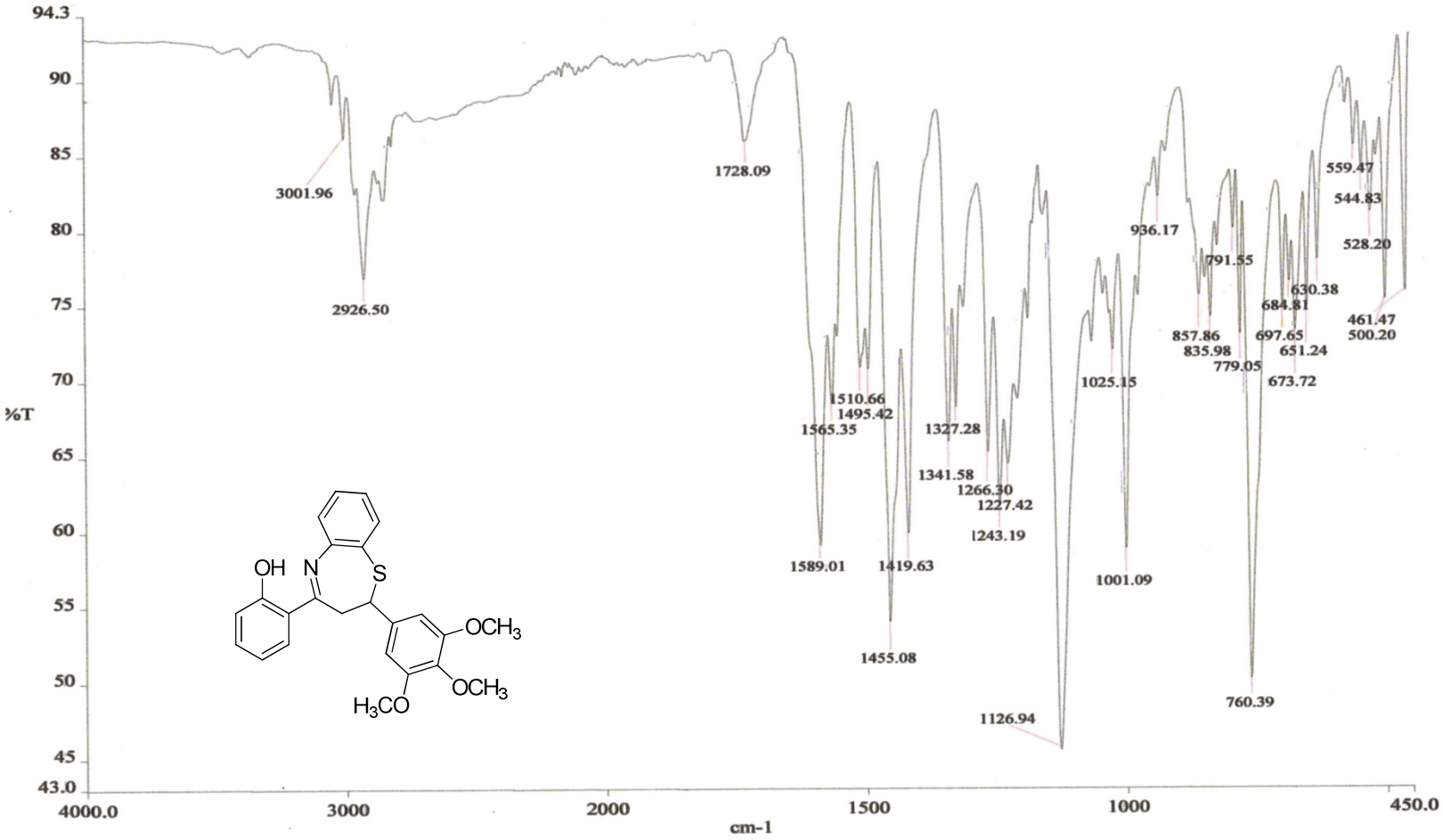
[1]HNMR of 2-(2-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA5



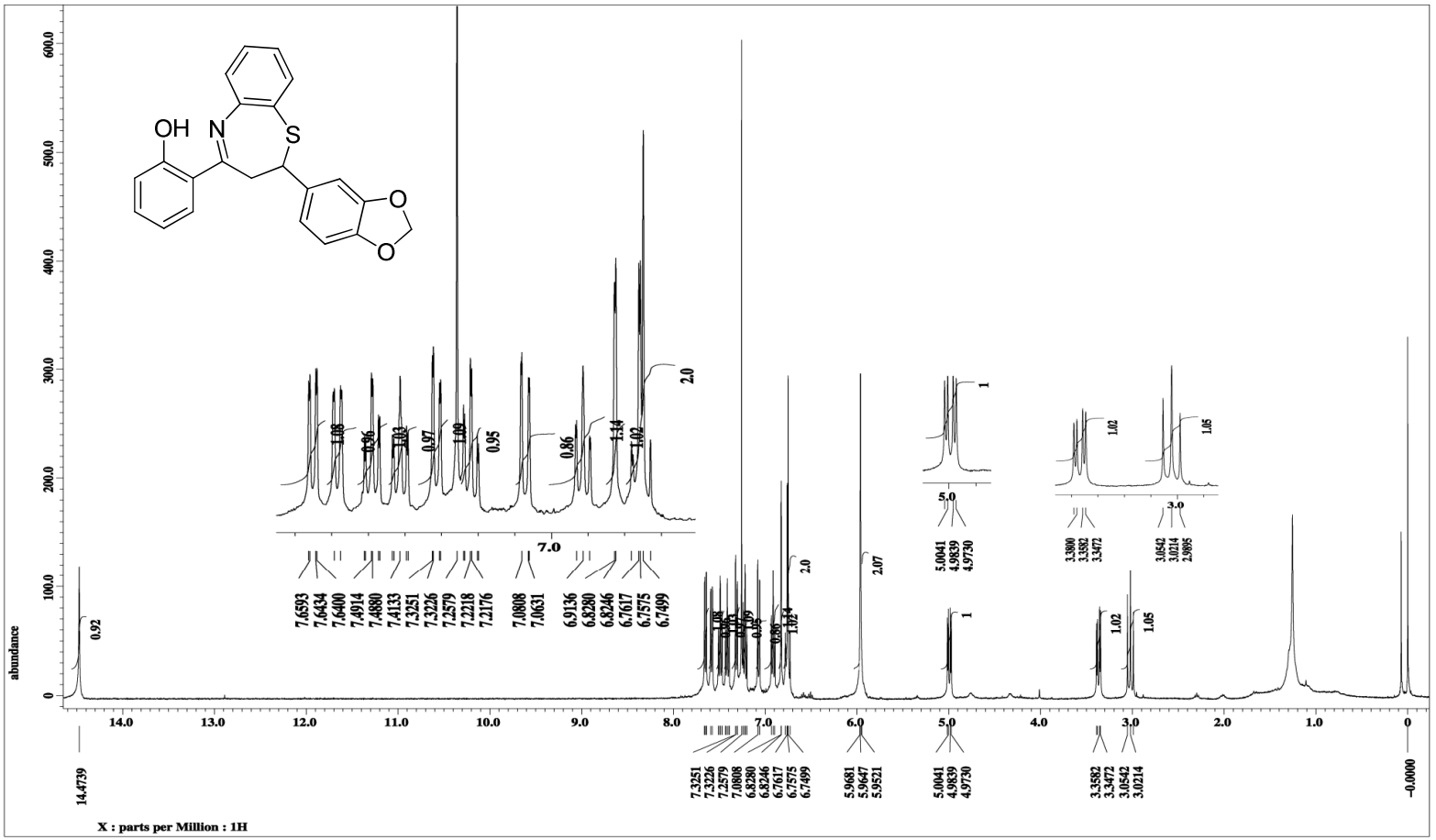
^{13}CNMR of 2-(2-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA5



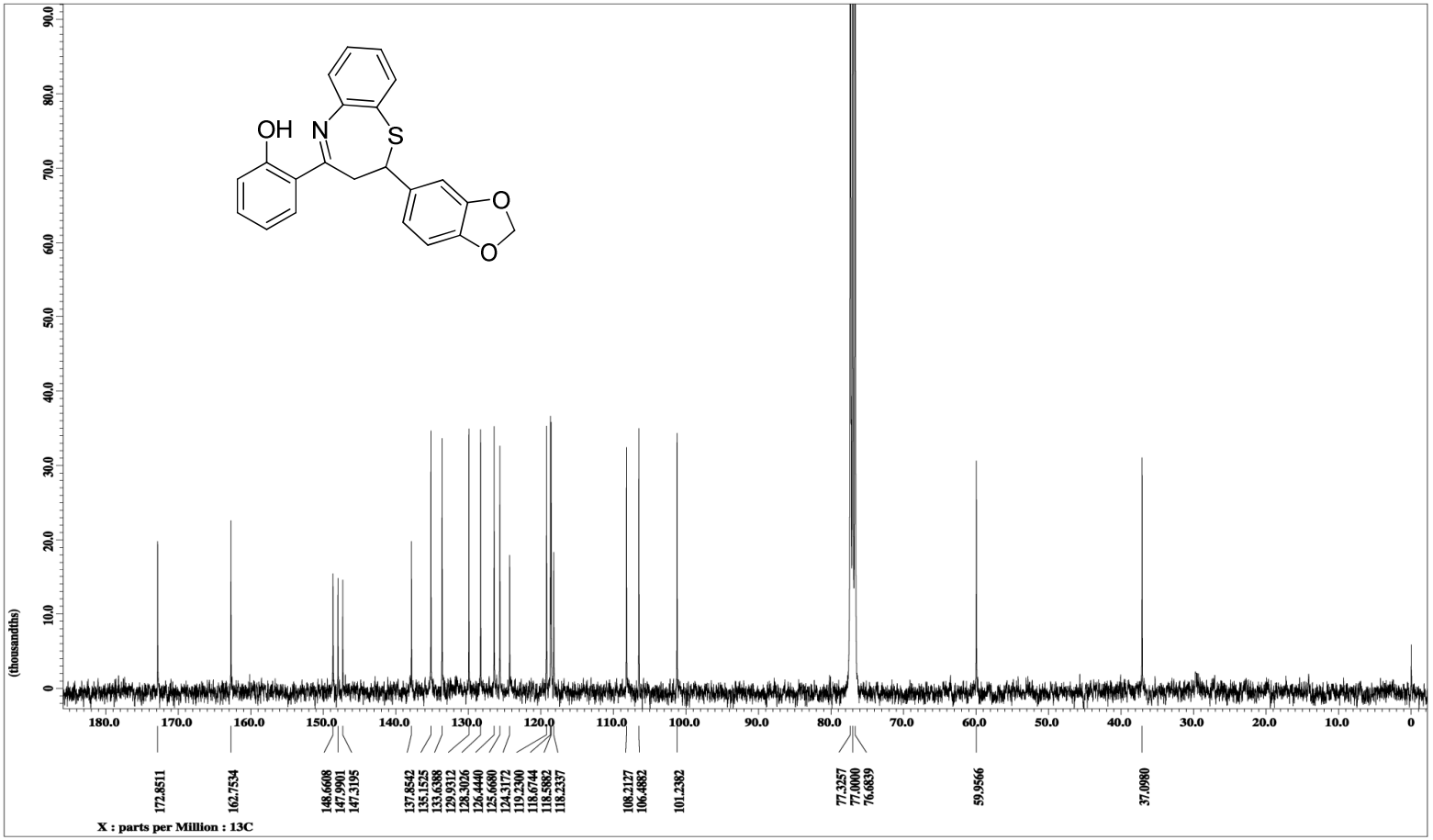
IR of 2-(2-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA5



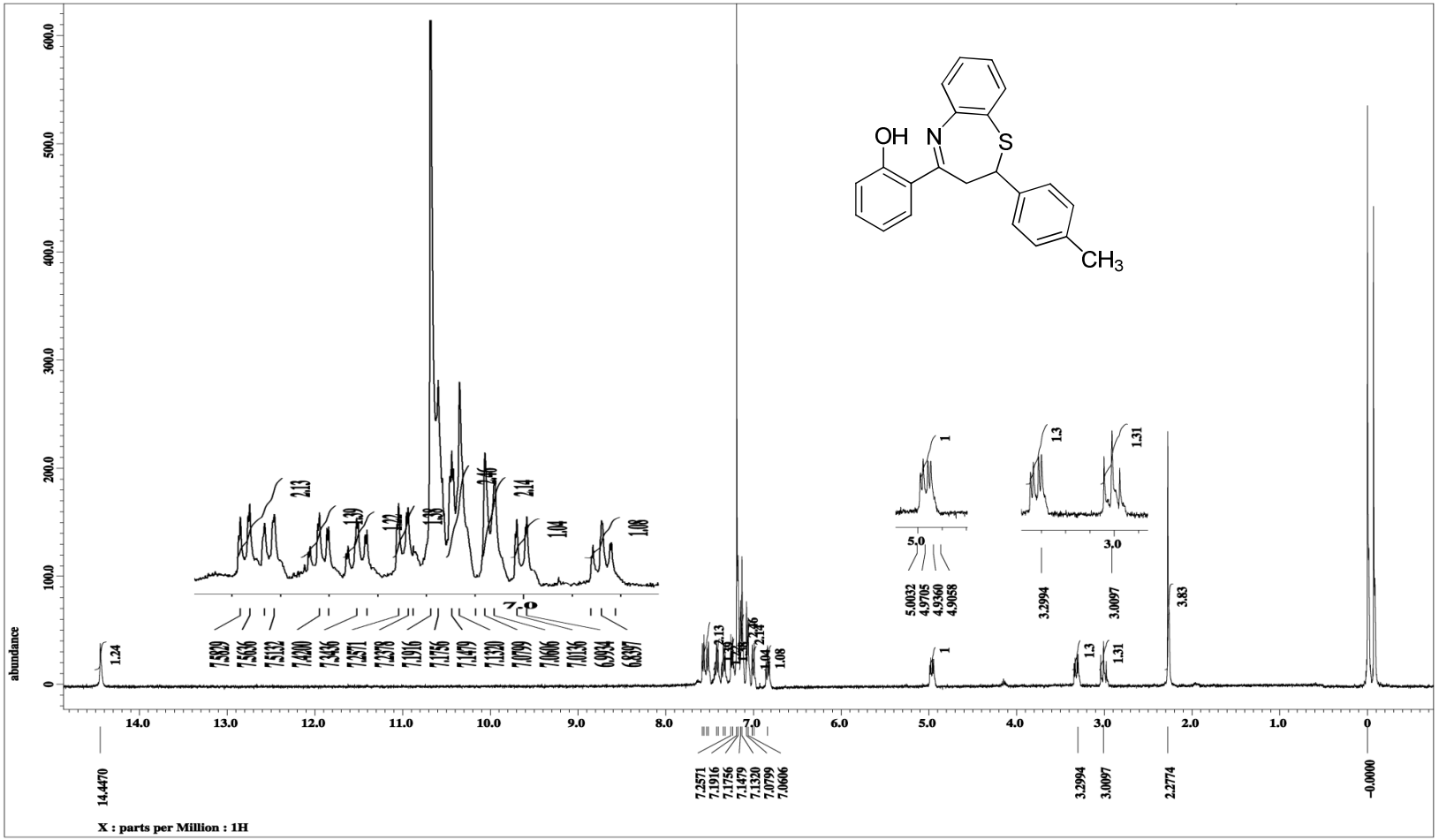
[1]HNMR of 2-(2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA6



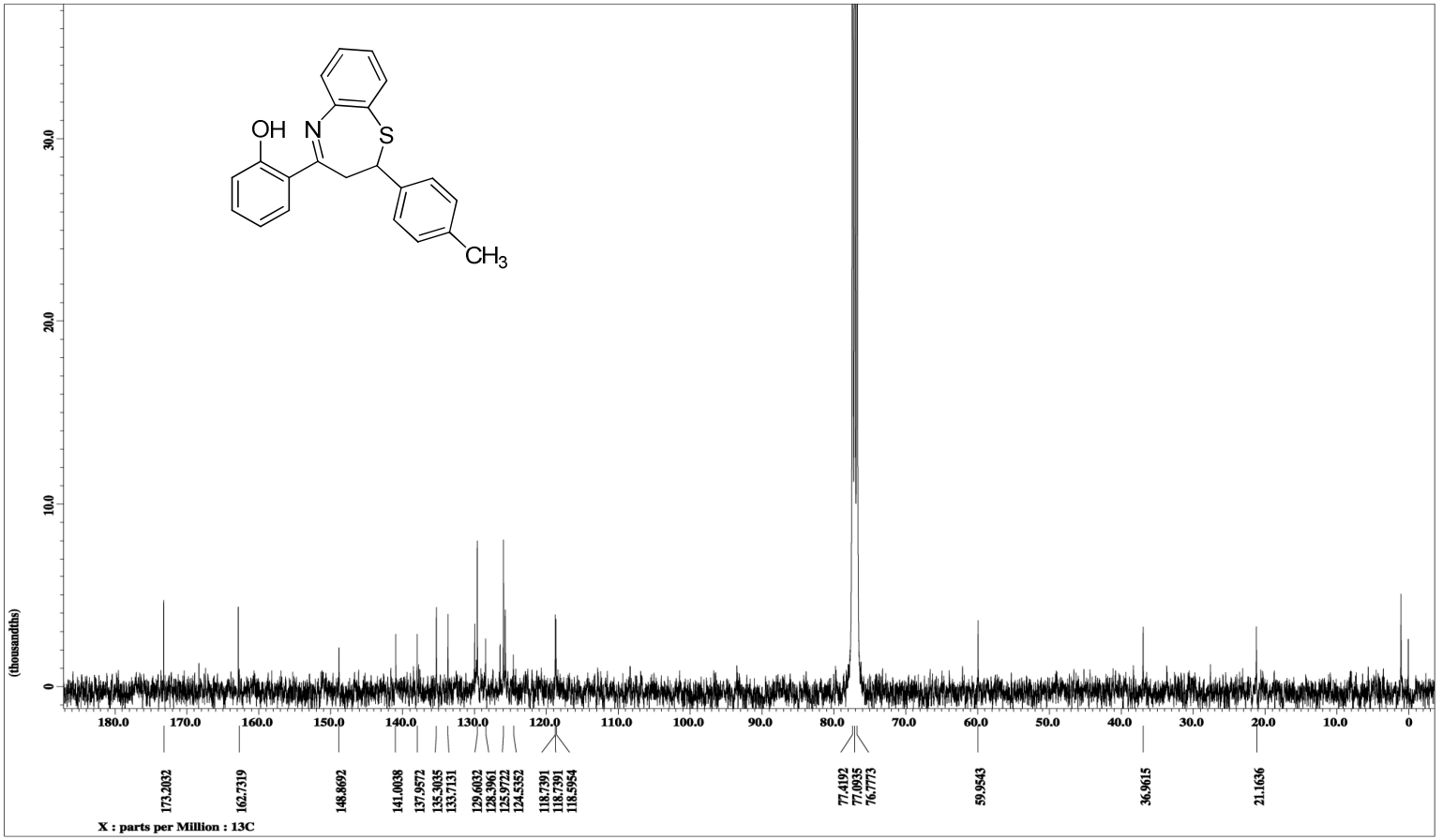
^{13}CNMR of 2-(2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA6



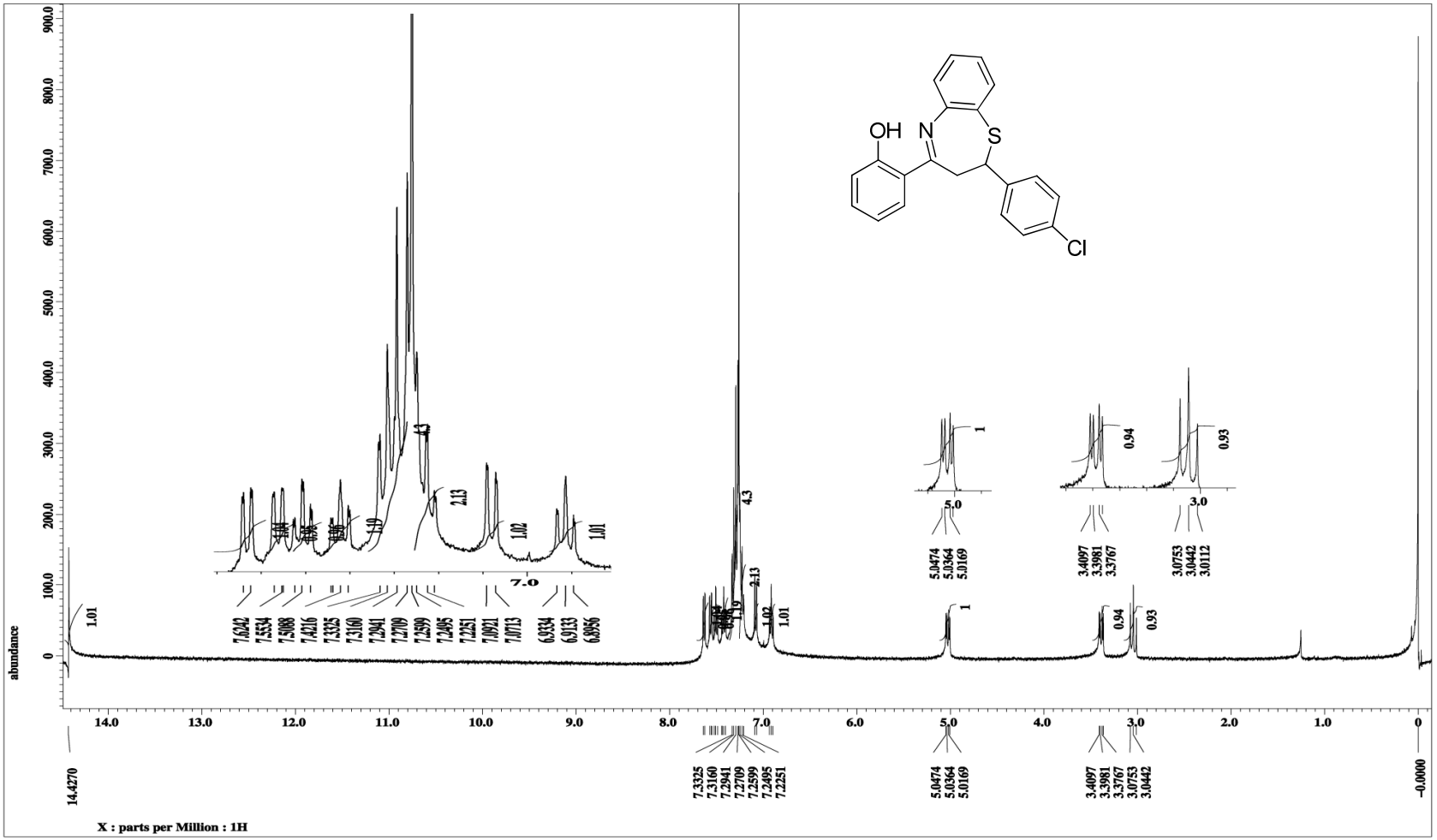
[1]HNMR of 2-(2-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA7



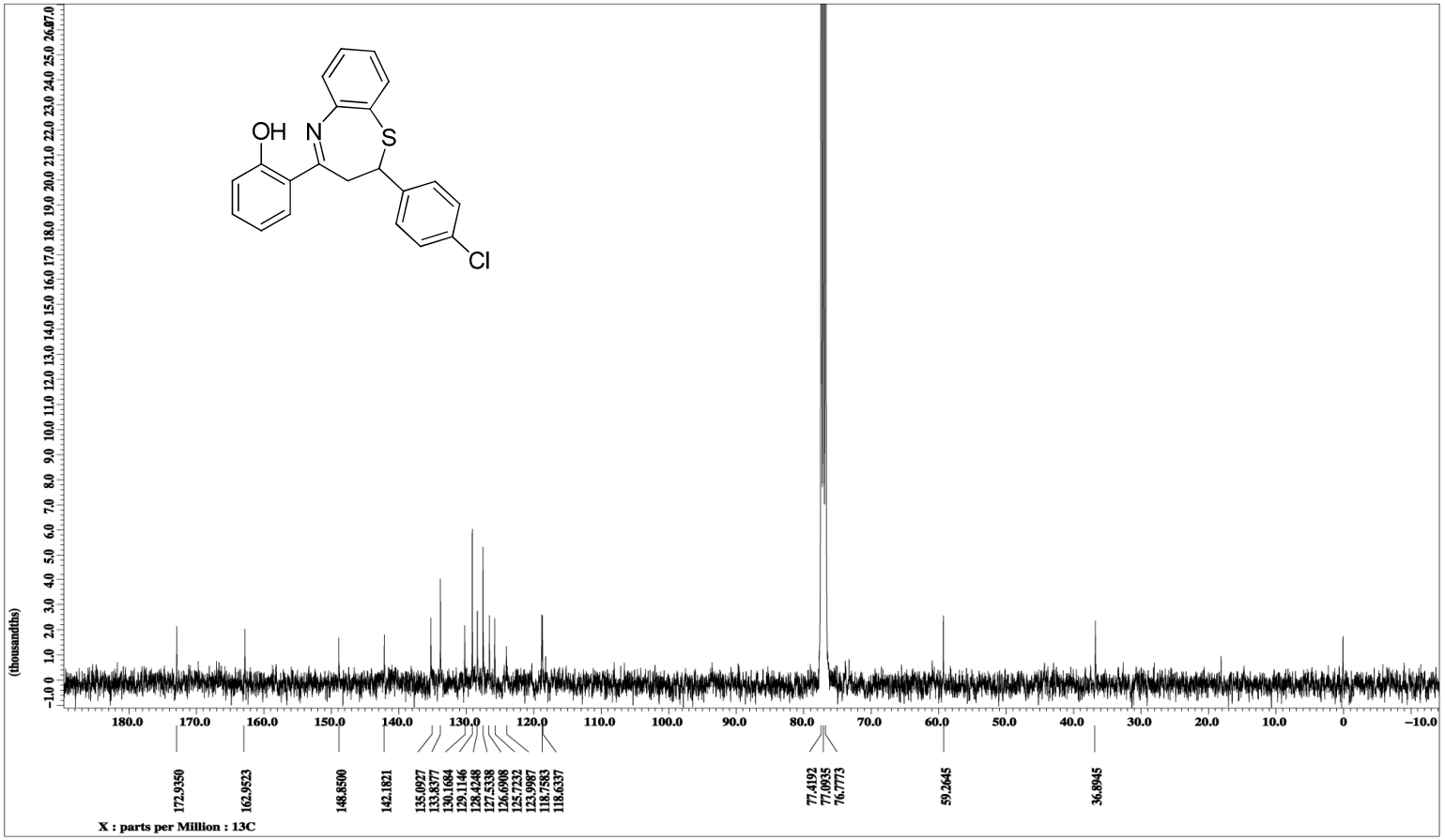
^{13}CNMR of 2-(2-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA7



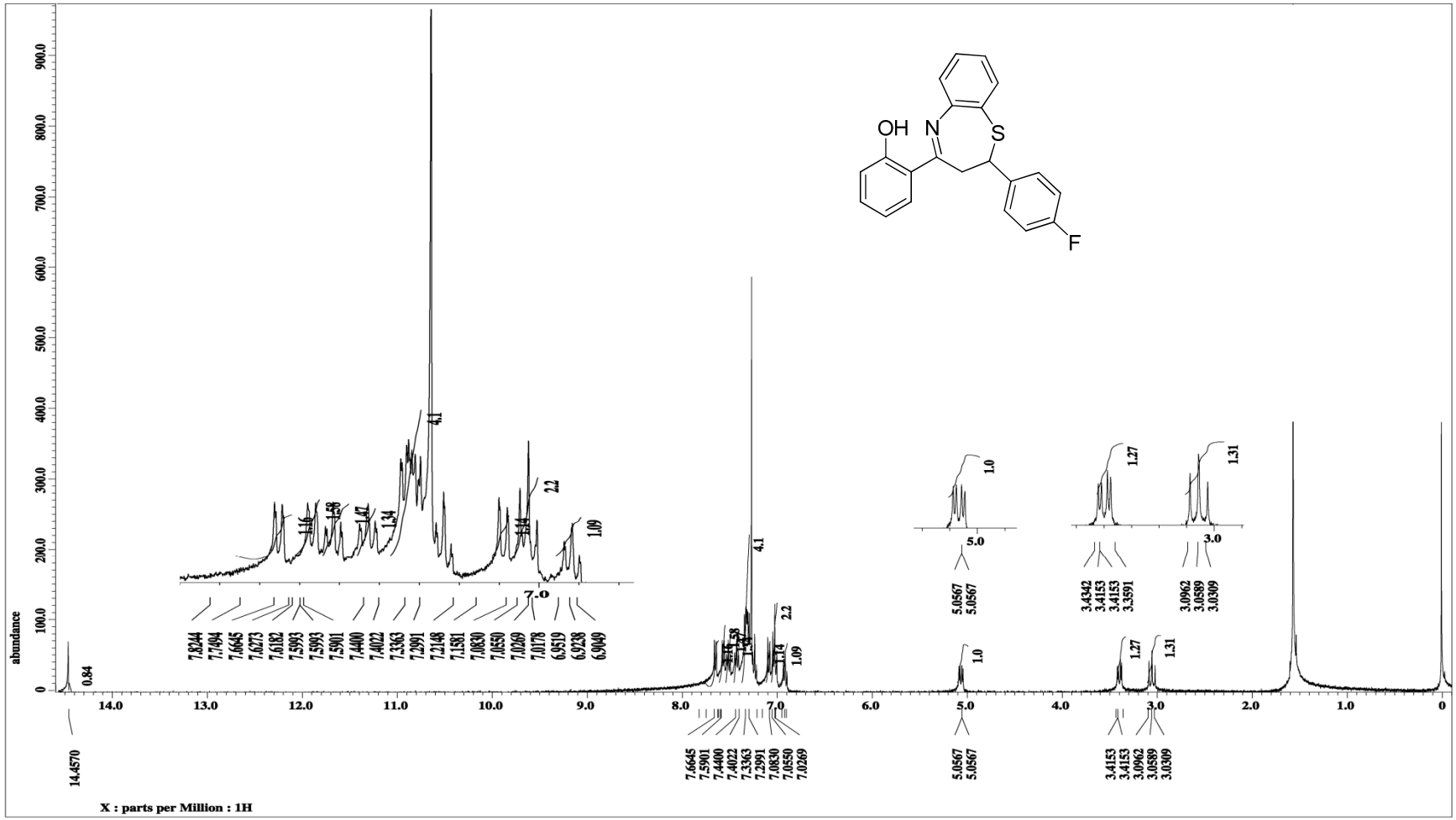
[1]HNMR of 2-(2-(4-chlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA8



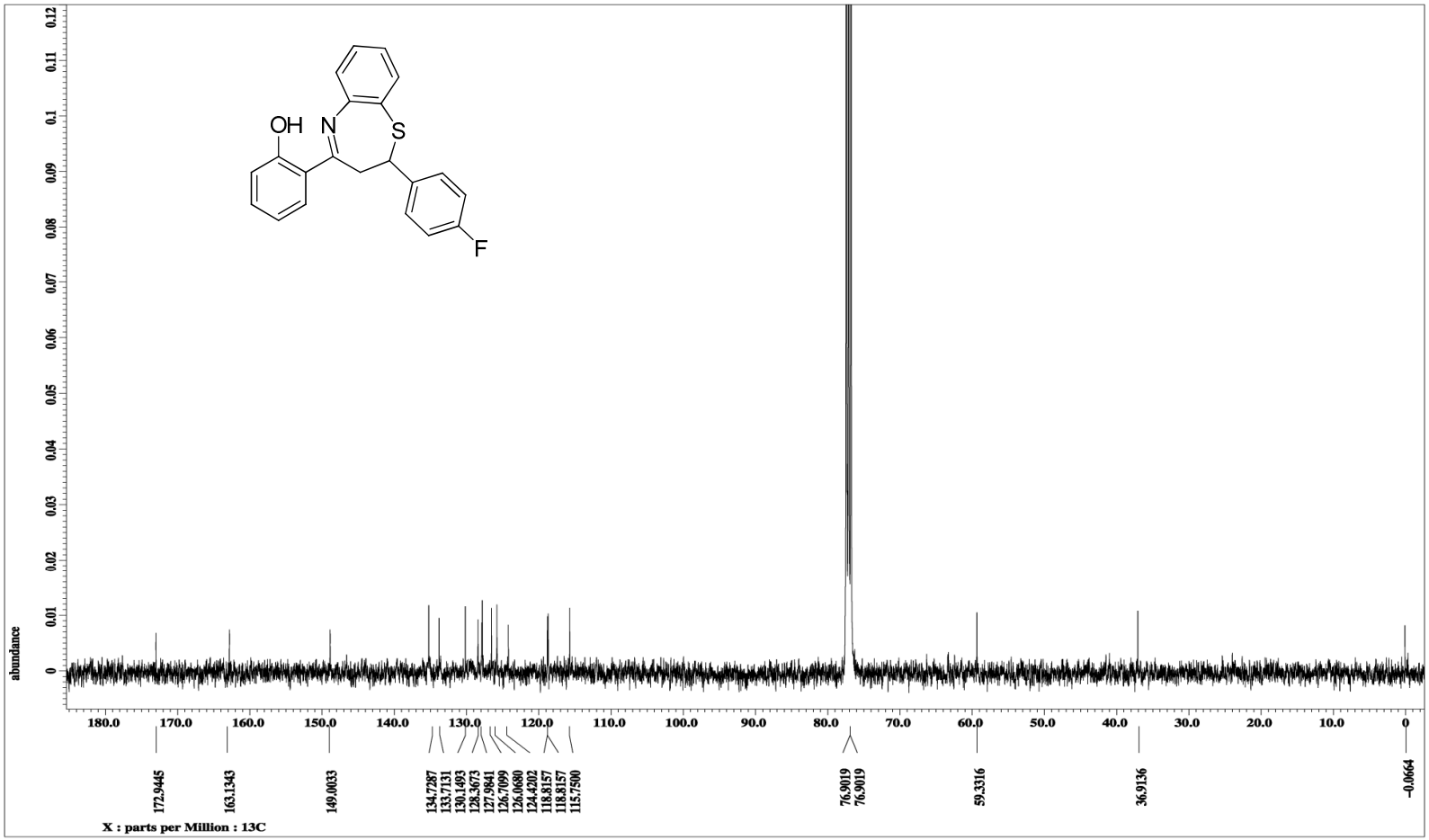
^{13}CNMR of 2-(2-(4-chlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA8



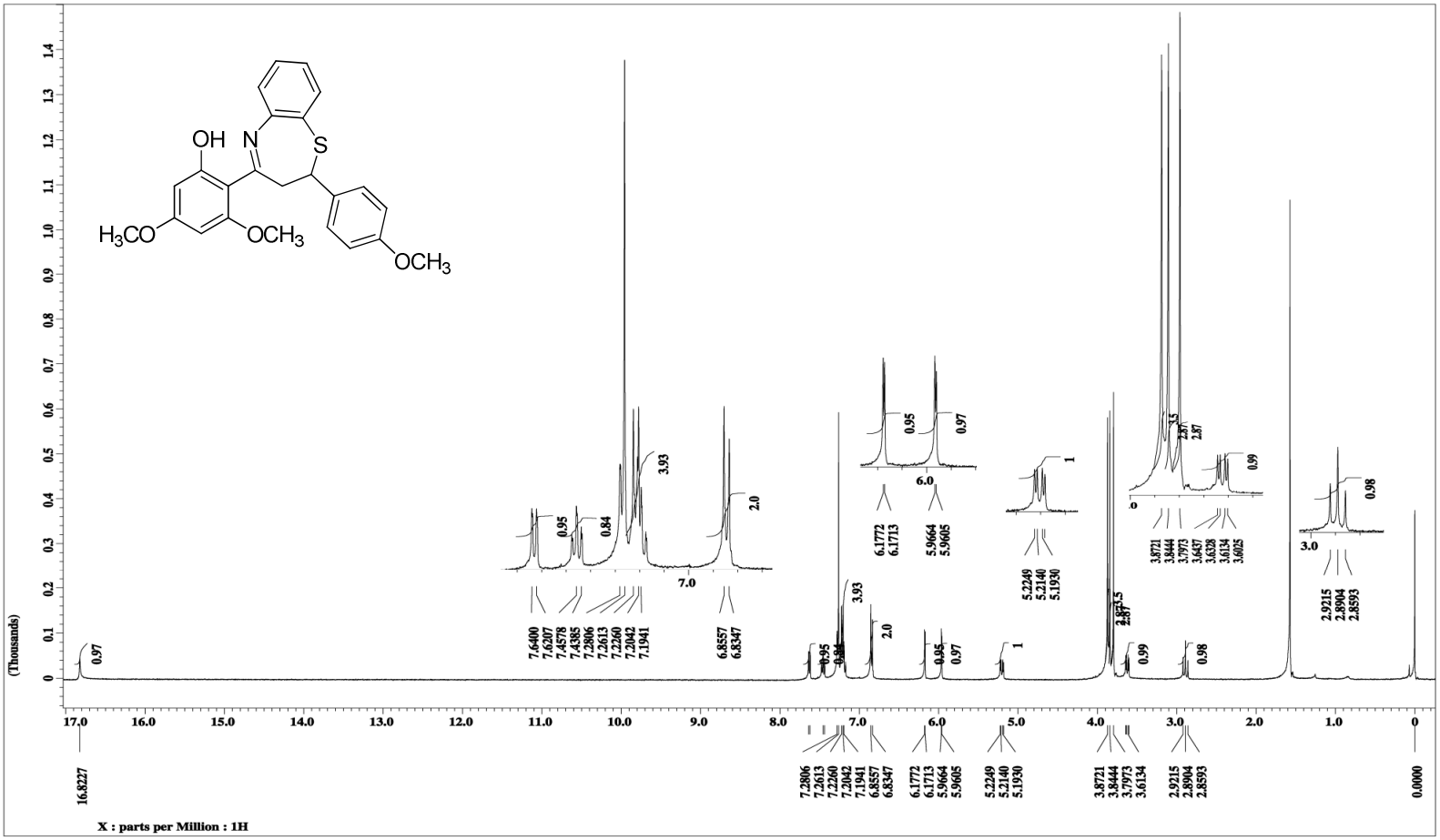
[1]HNMR of 2-(2-(4-fluorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA9



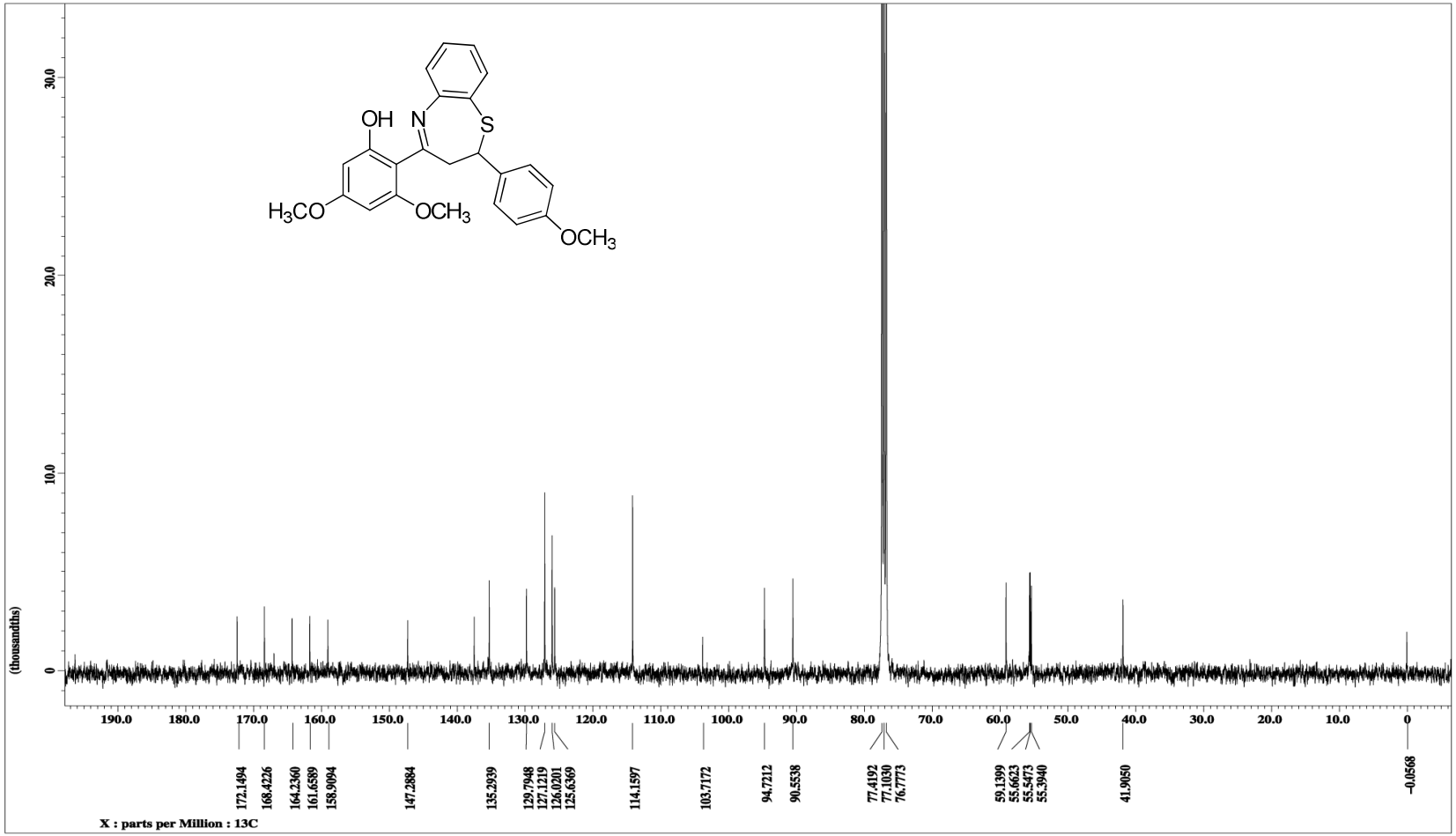
^{13}CNMR of 2-(2-(4-fluorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA9



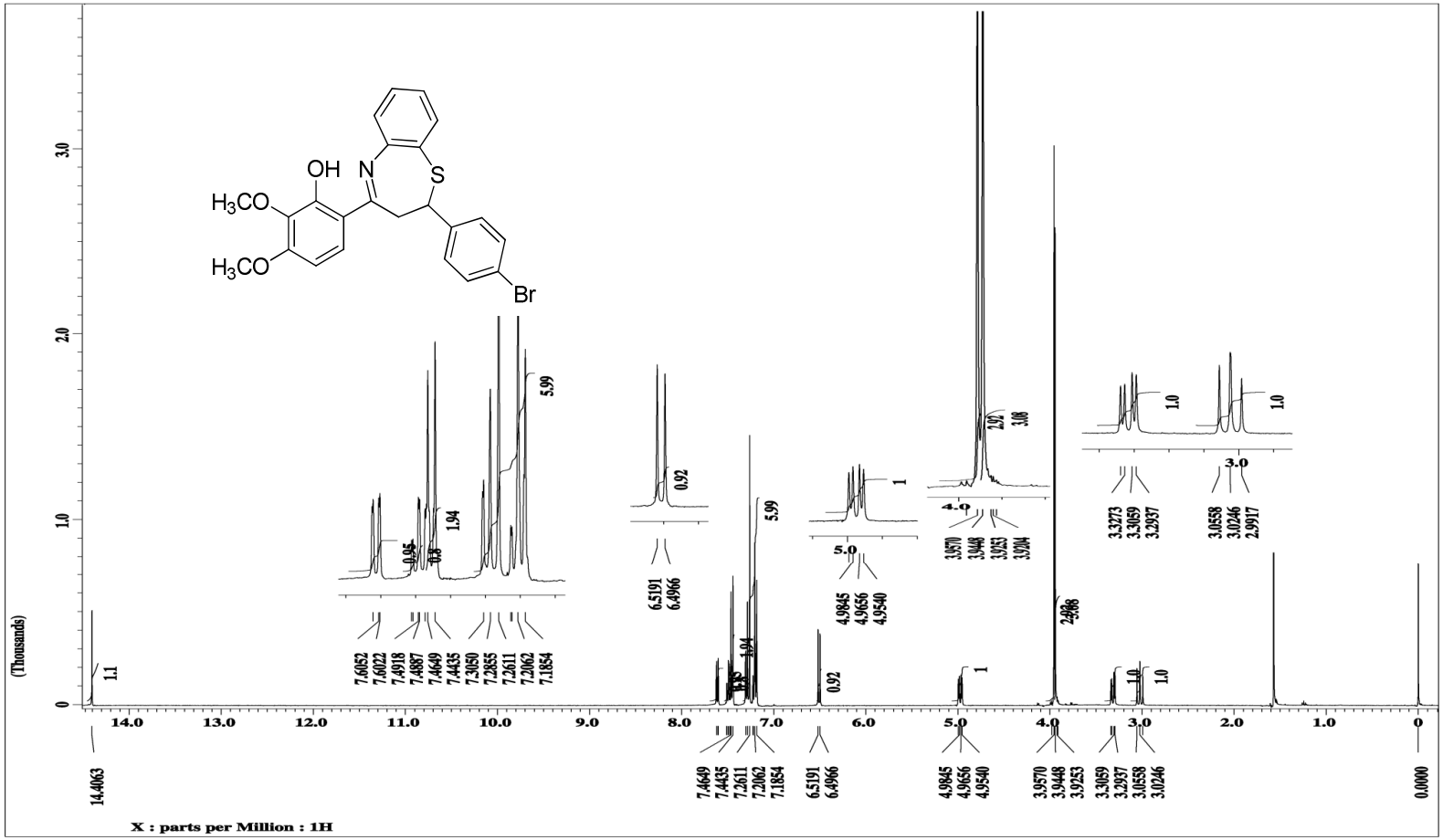
[1]HNMR of 3, 5-dimethoxy-2-(2-(4-methoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA10



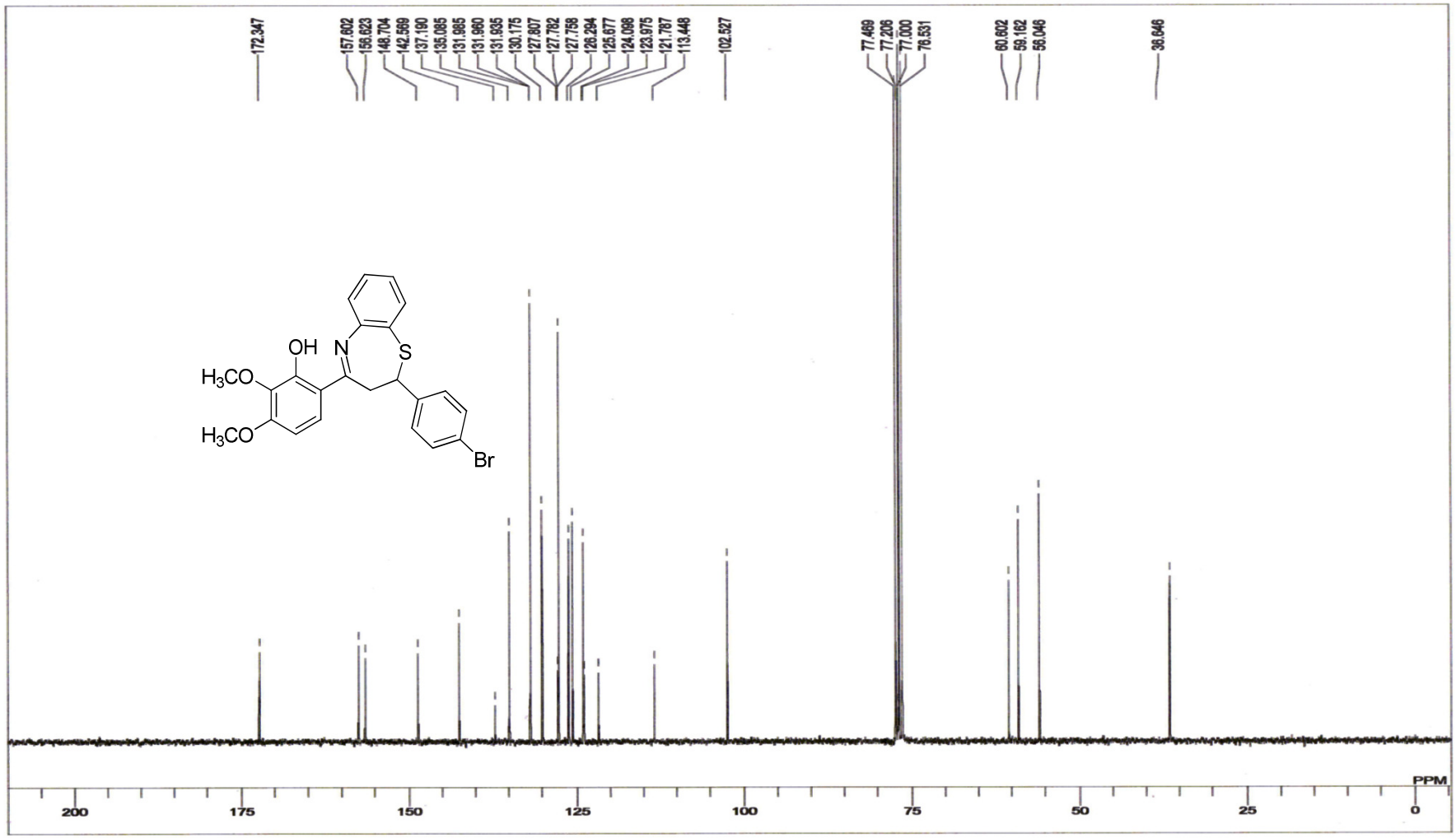
^{13}CNMR of 3, 5-dimethoxy-2-(2-(4-methoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol MA10



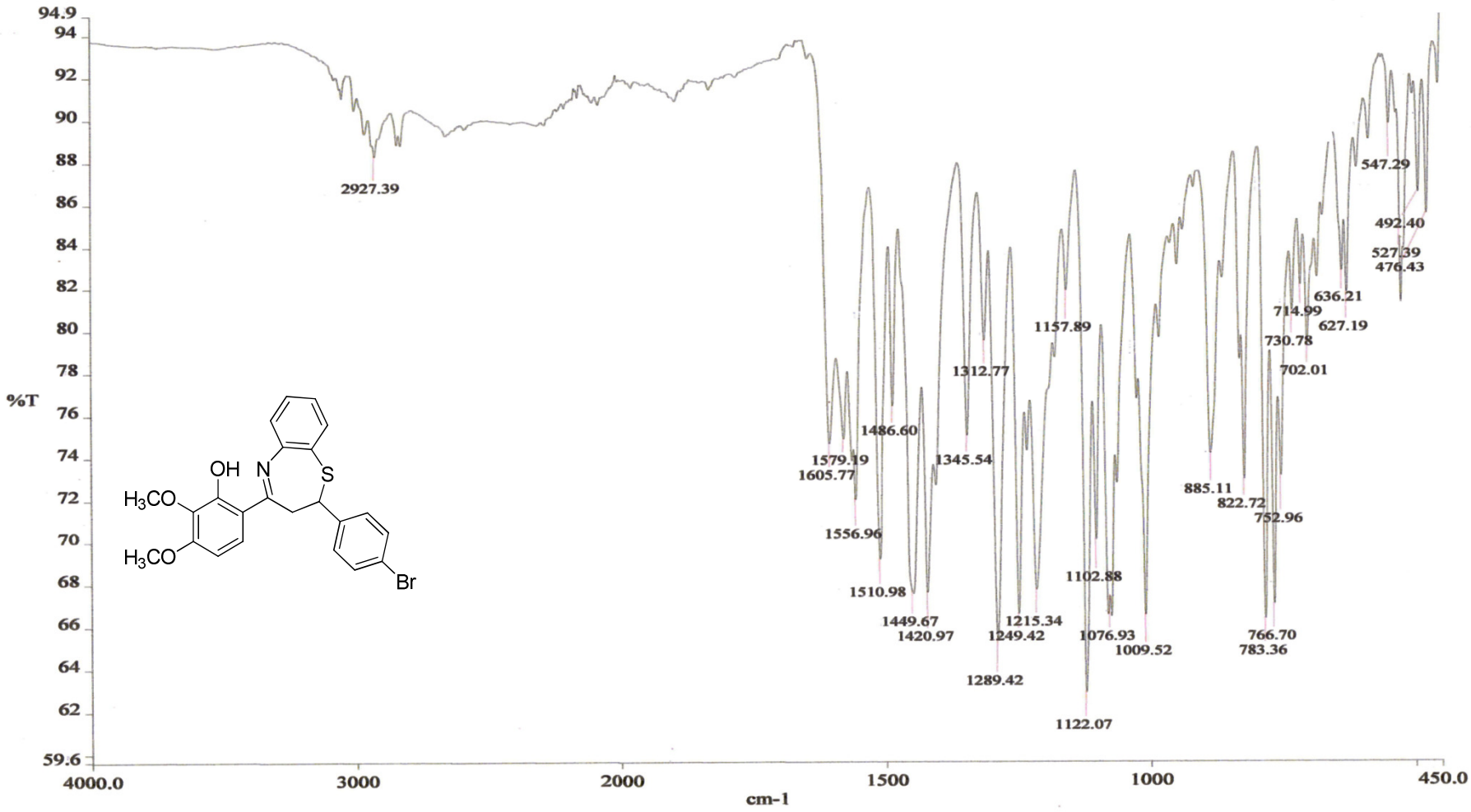
[1]HNMR of 6-(2-(4-bromophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)-2,3-dimethoxyphenol MA11



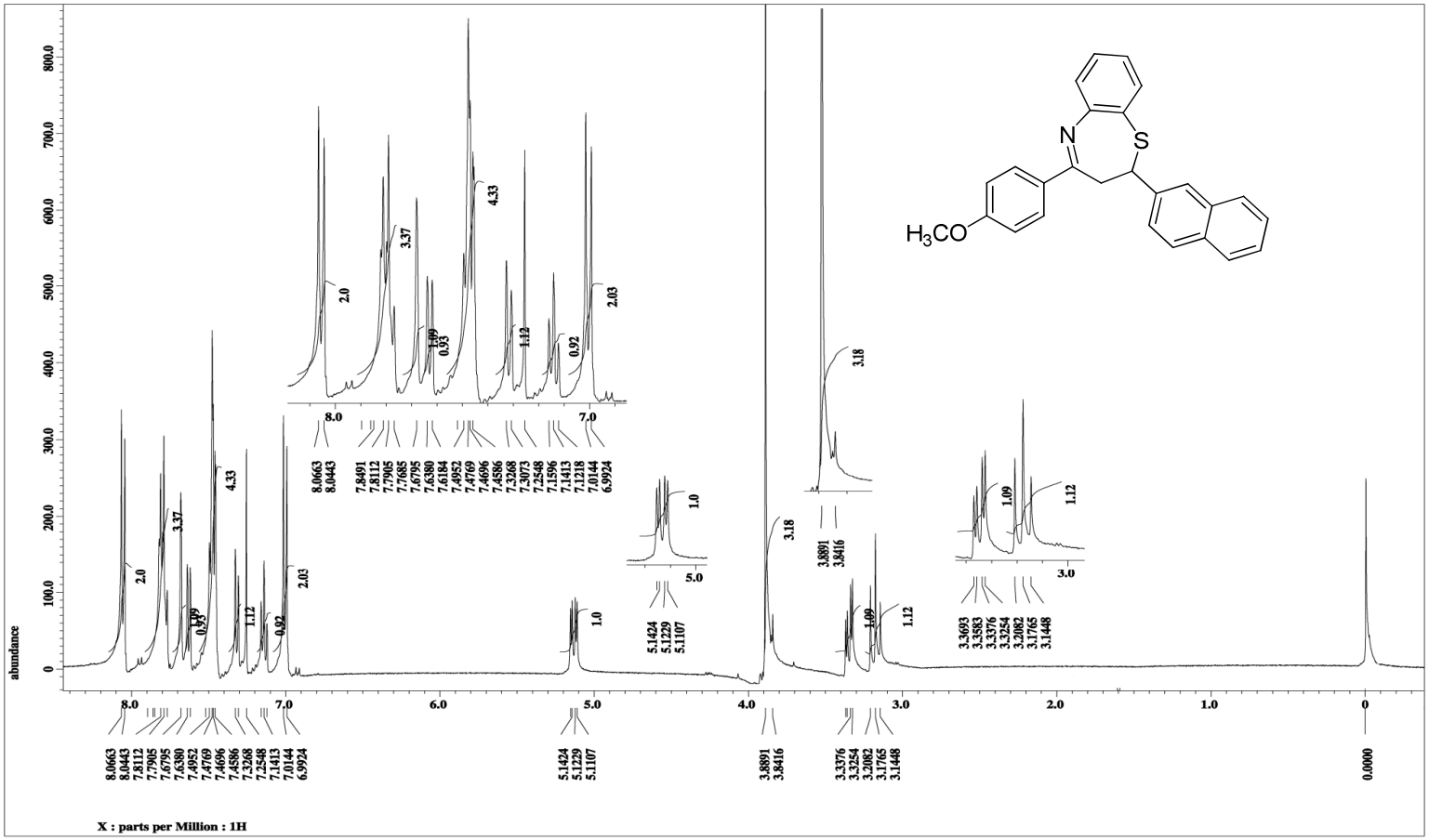
^{13}CNMR of 6-(2-(4-bromophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)-2,3-dimethoxyphenol MA11



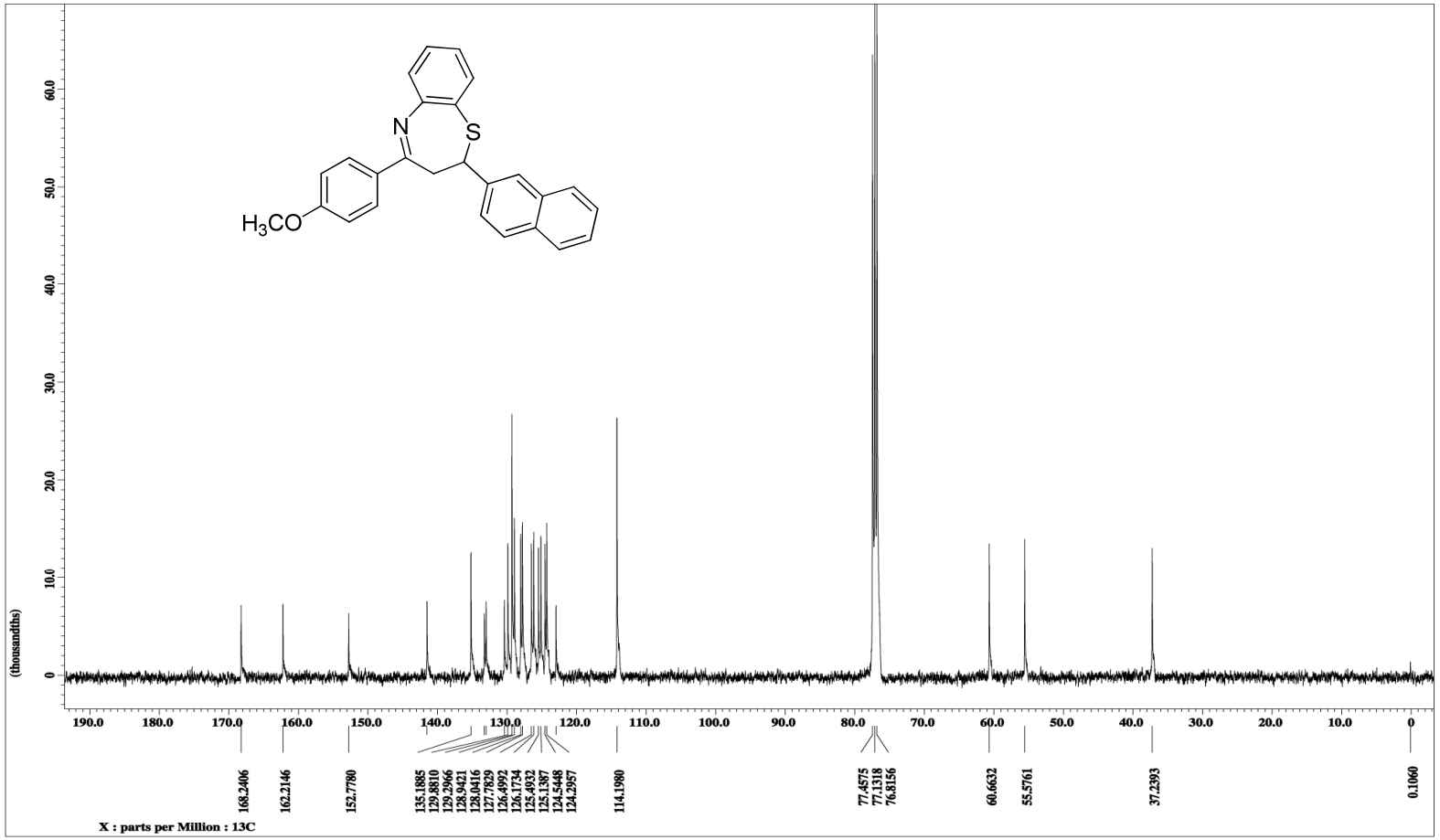
IR of 6-(2-(4-bromophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)-2,3-dimethoxyphenol MA11



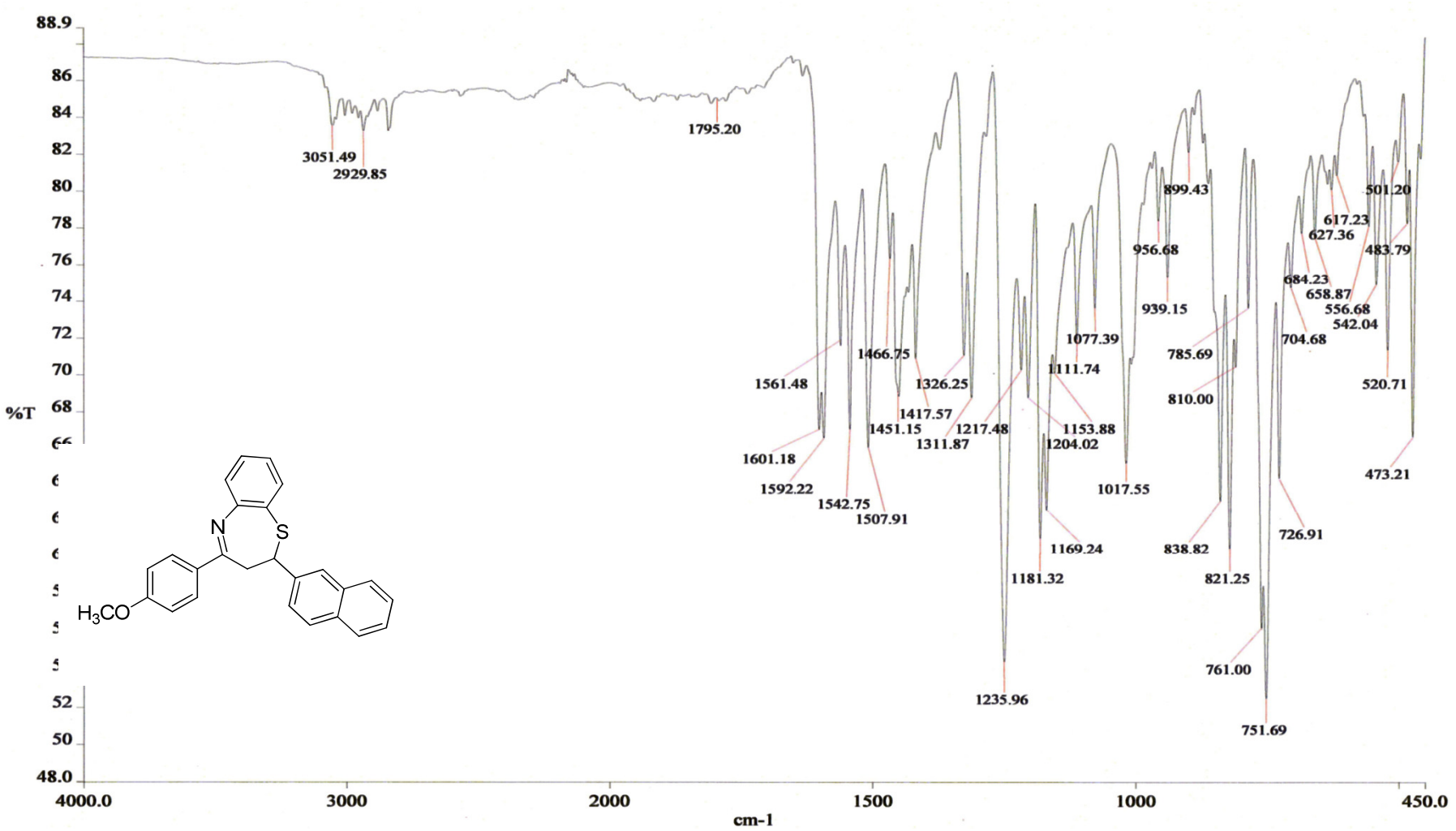
[1]HNMR of 4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine MA12



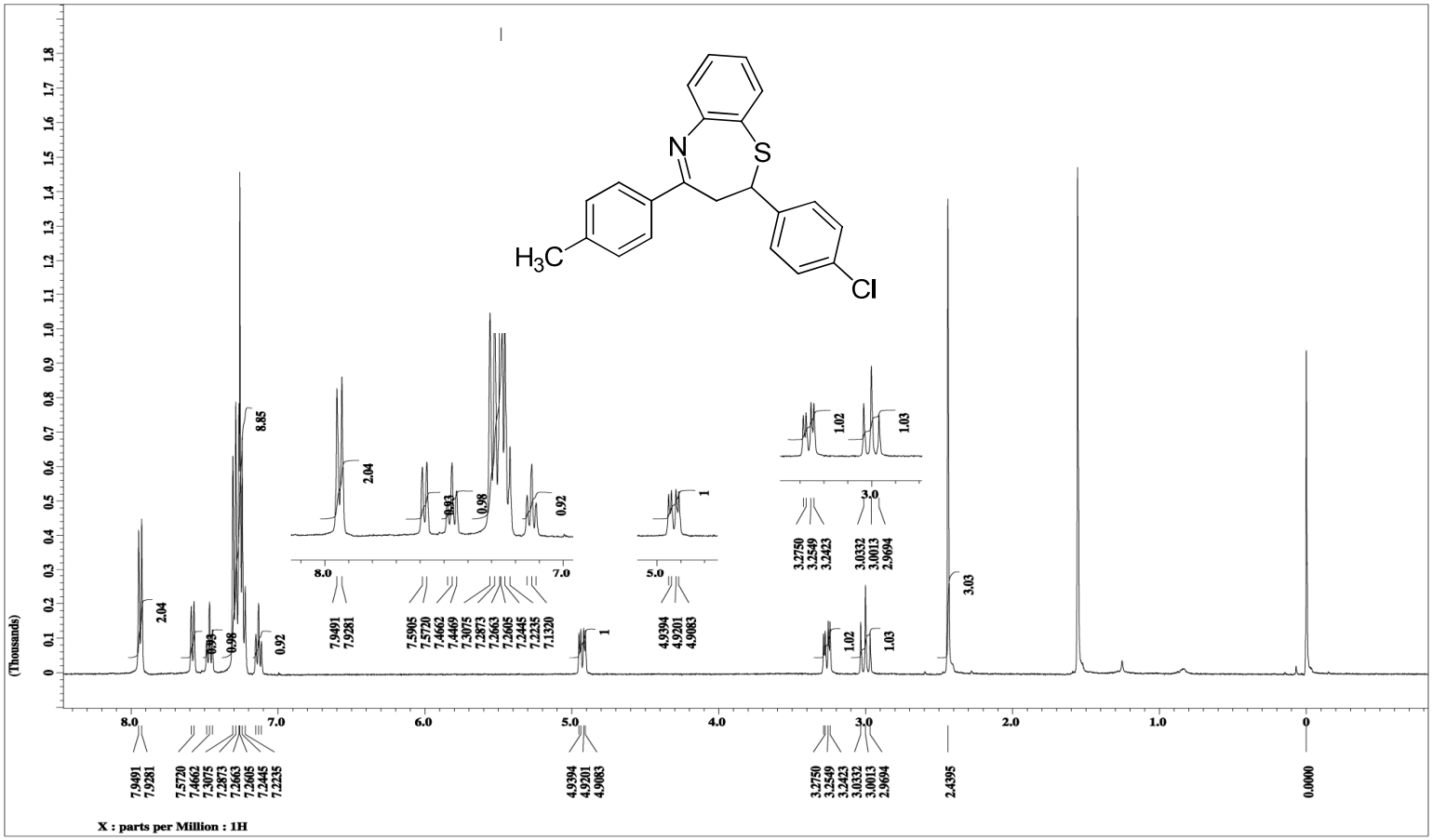
^{13}CNMR of 4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine MA12



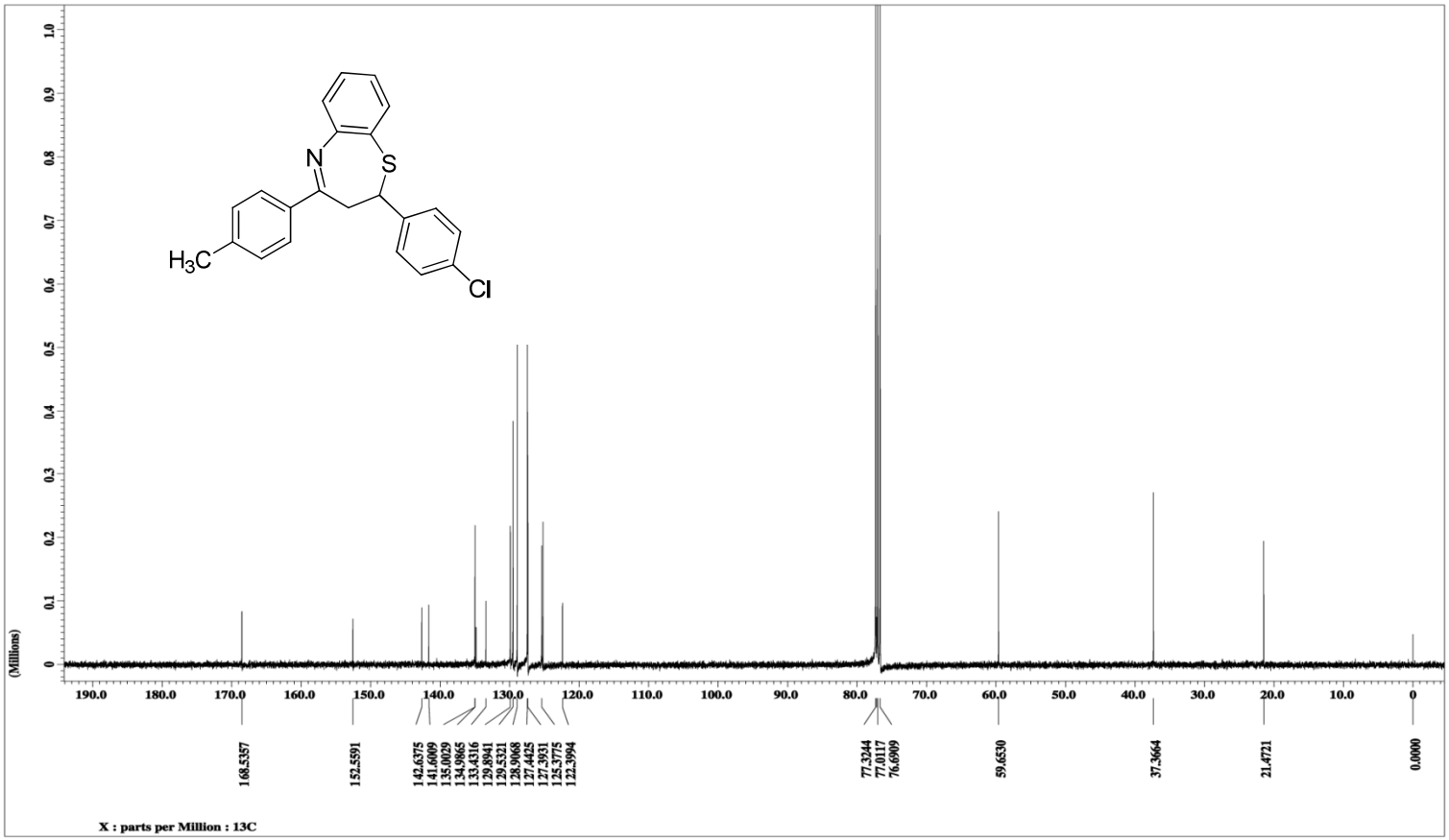
IR of 4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine MA12



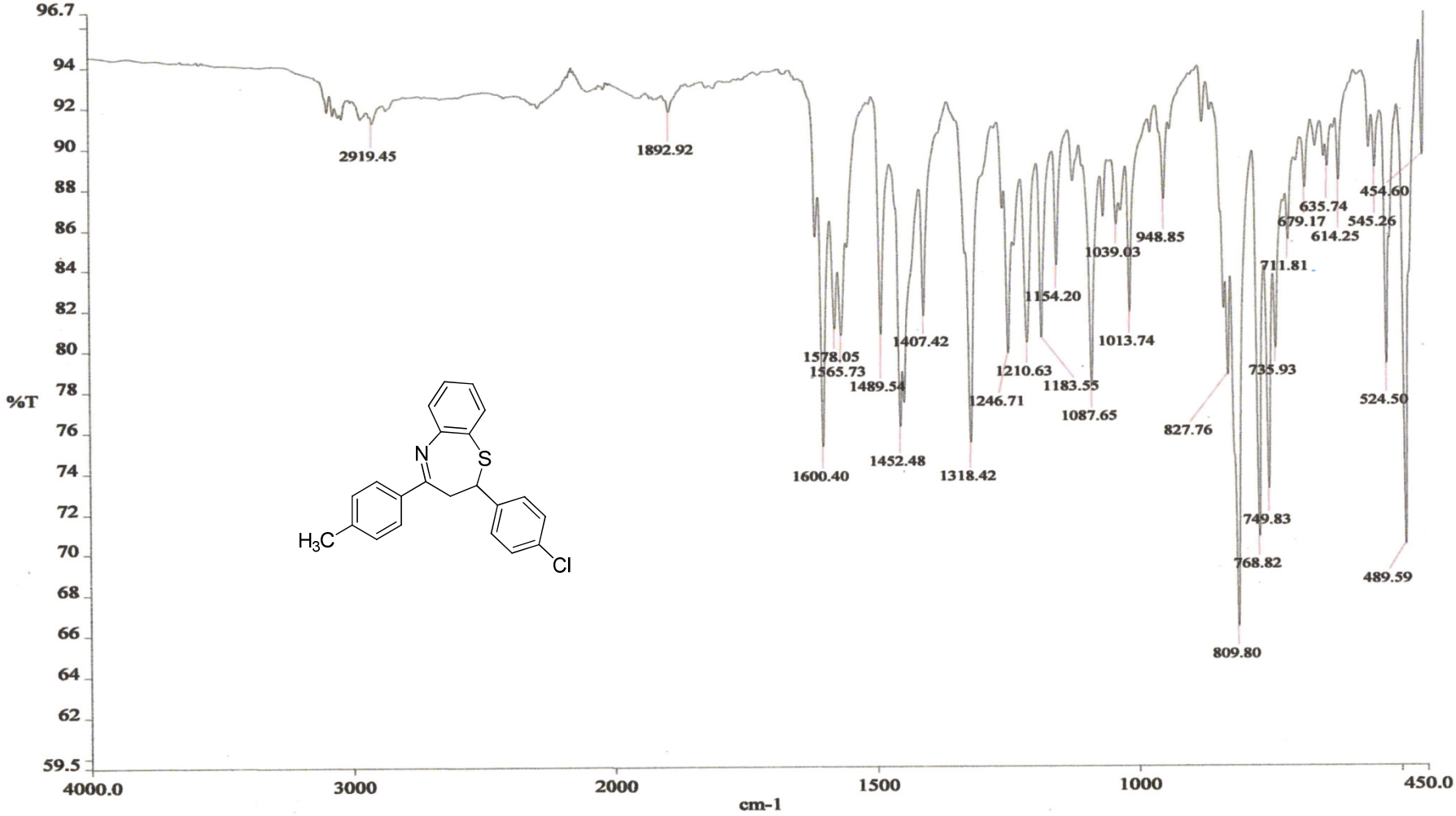
[1]HNMR of 2-(4-chlorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA13



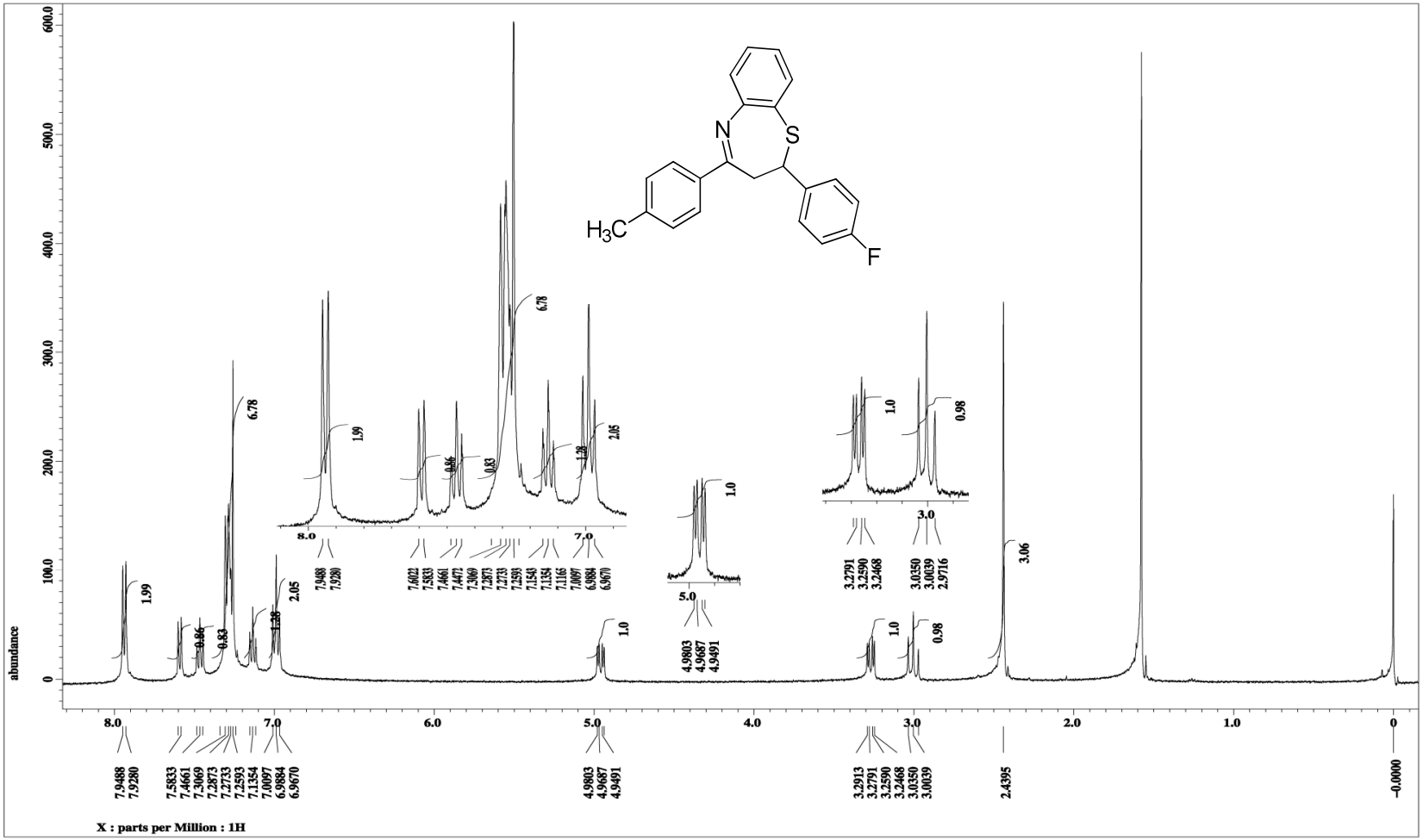
^{13}CNMR of 2-(4-chlorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA13



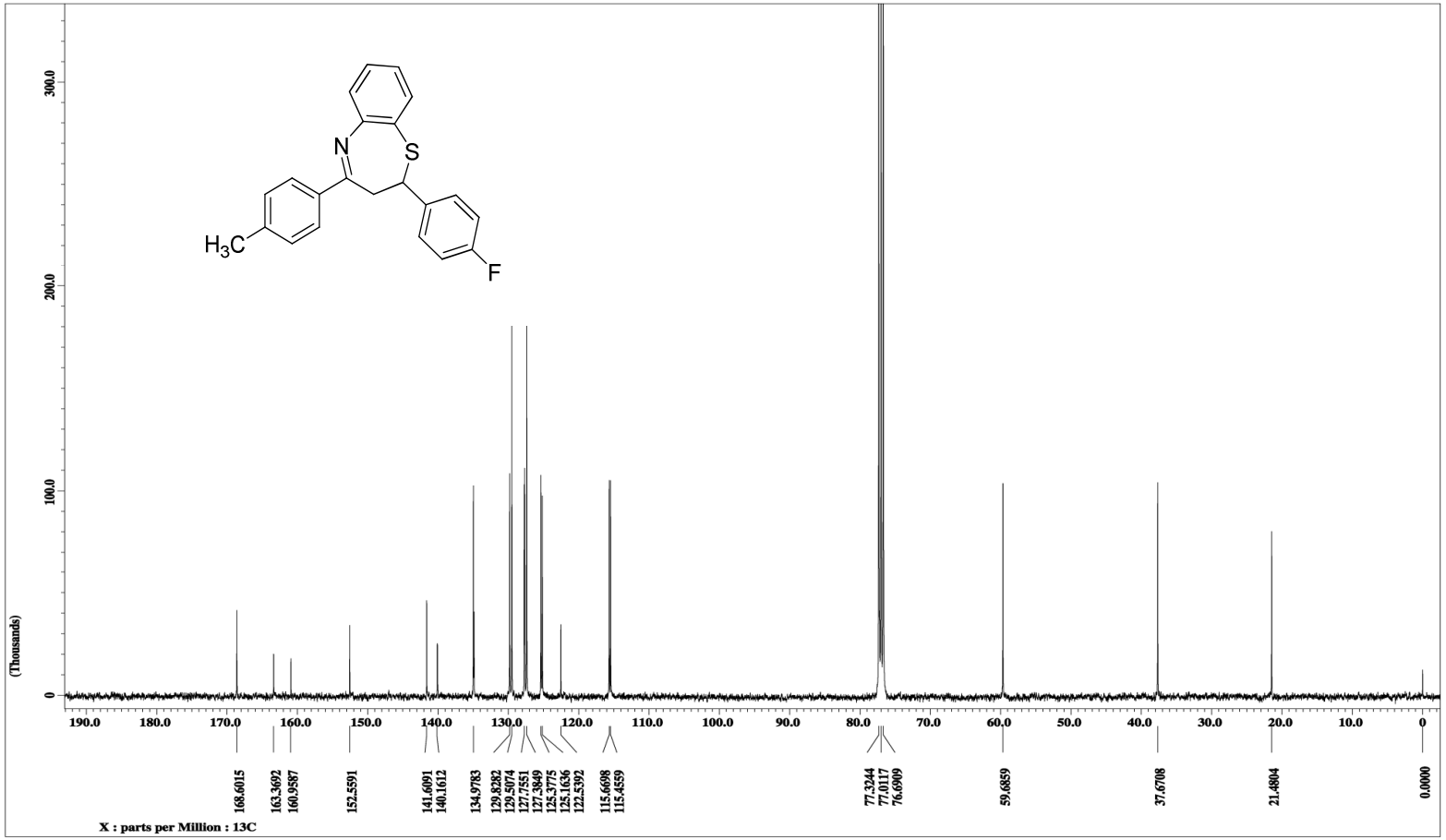
IR of 2-(4-chlorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA13



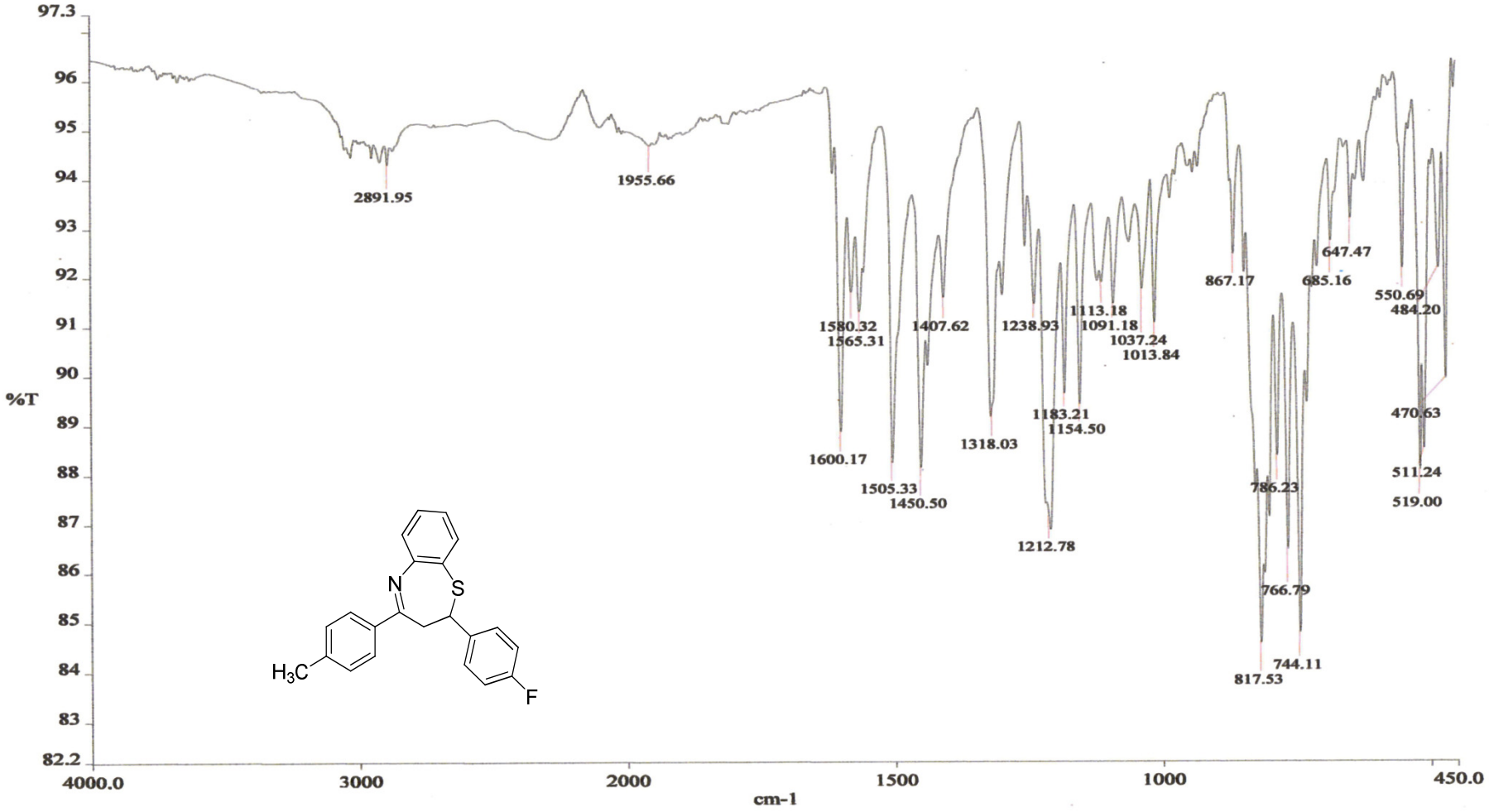
[1]HNMR of 2-(4-fluorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA14



^{13}CNMR of 2-(4-fluorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA14

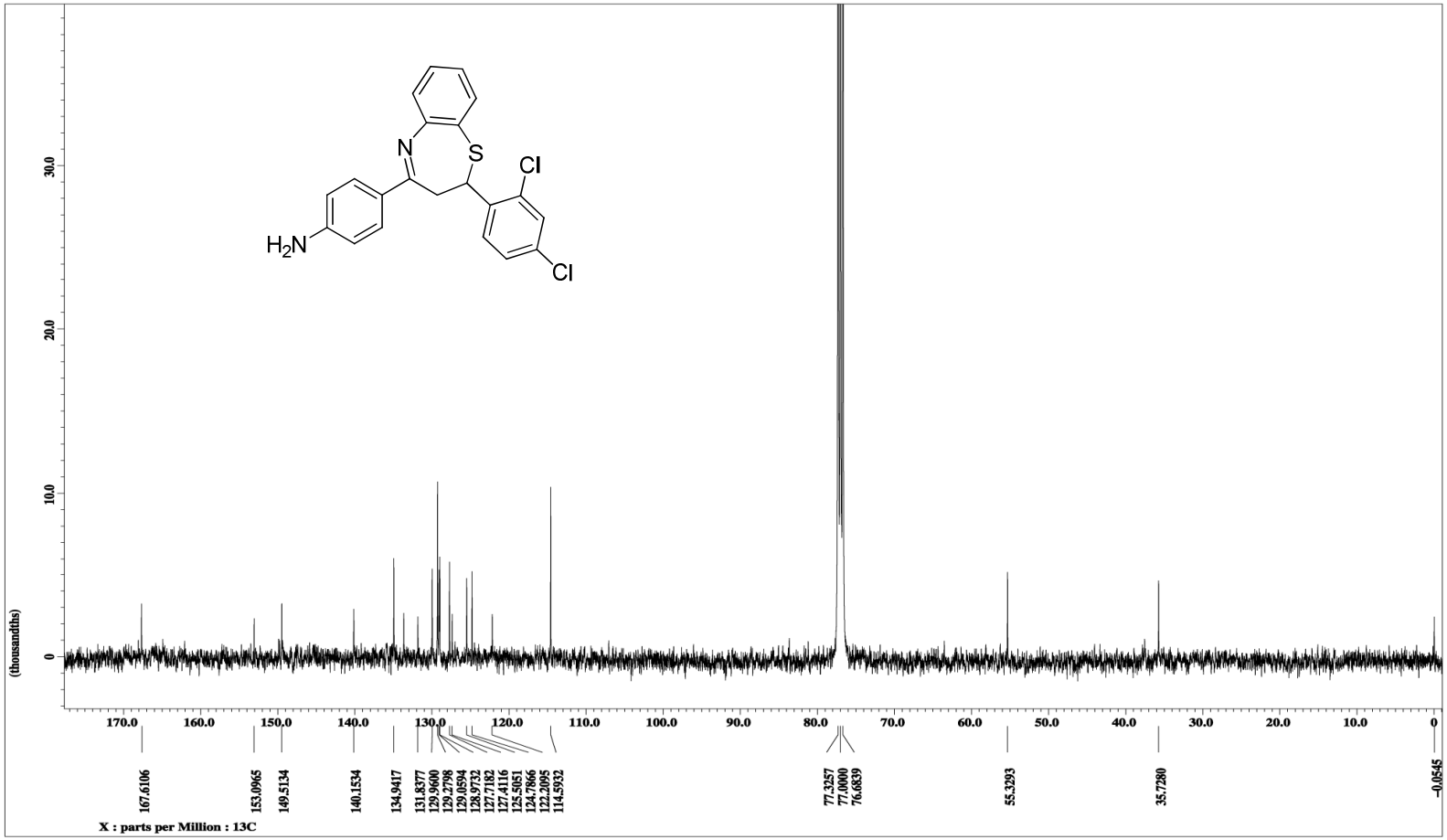


IR of 2-(4-fluorophenyl)-4-p-tolyl-2, 3-dihydrobenzo[b][1,4]thiazepine MA14

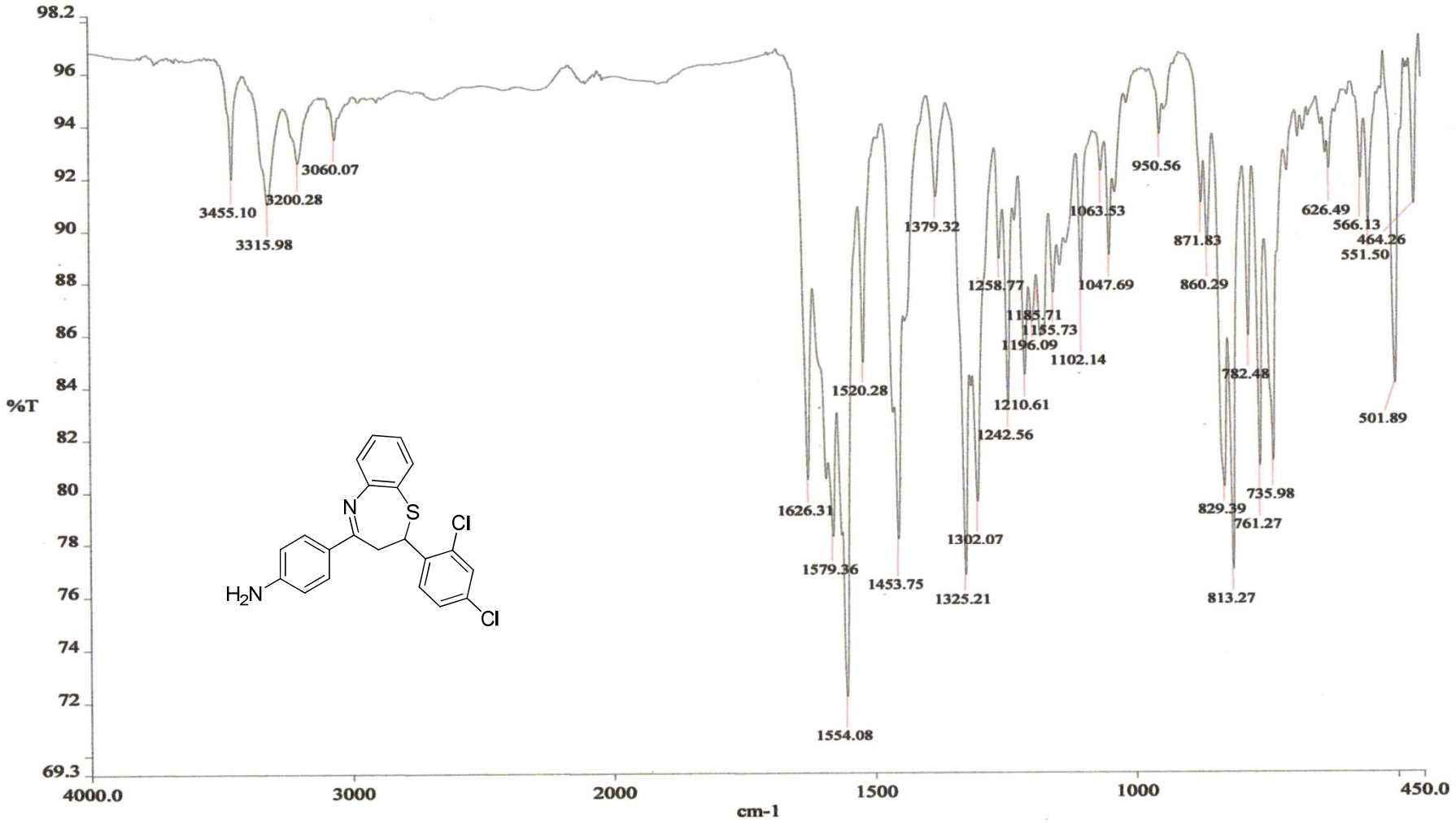


[1]HNMR of 4-(2-(2, 4-dichlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)aniline MA15

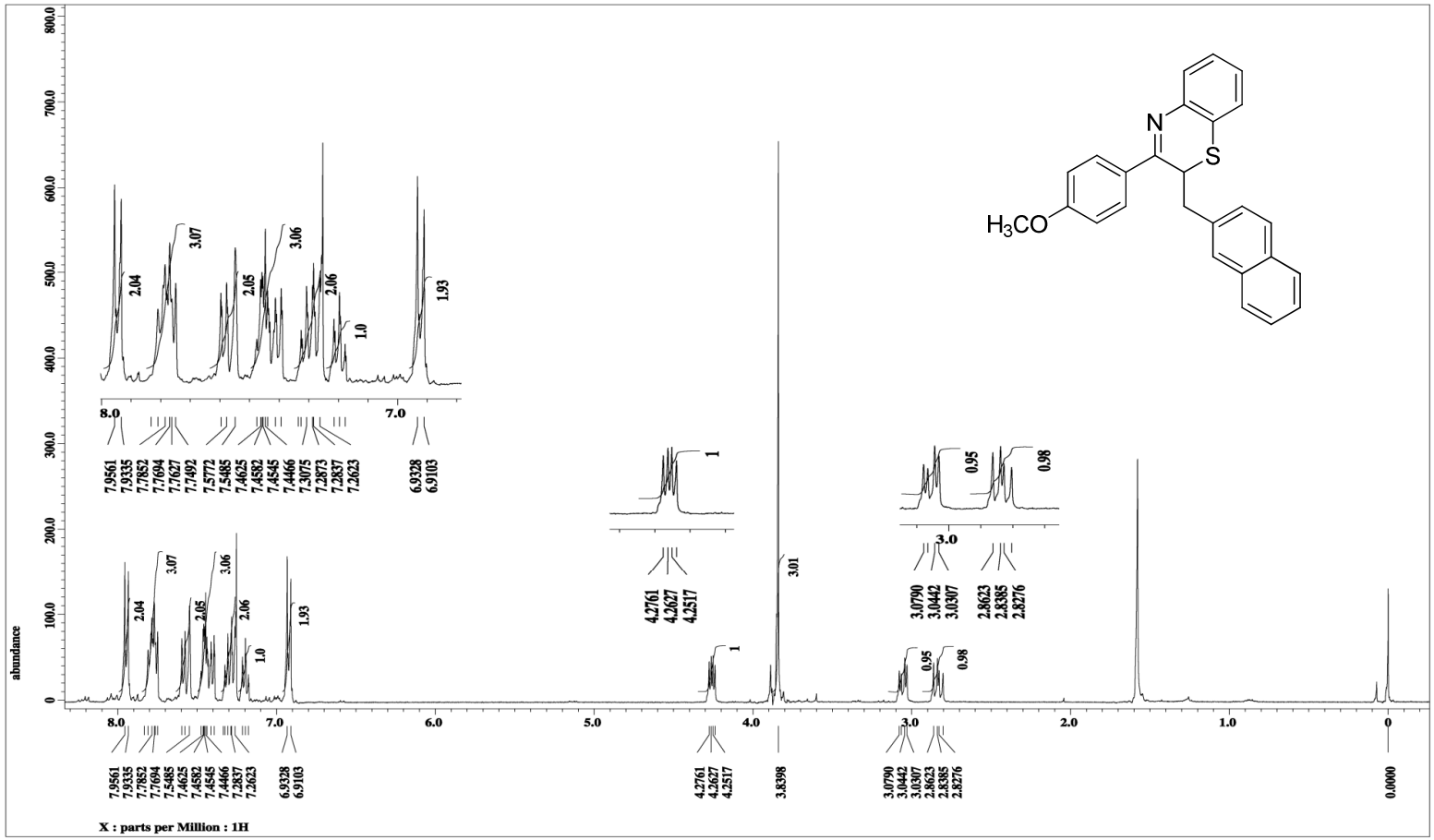
^{13}CNMR of 4-(2-(2, 4-dichlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)aniline MA15



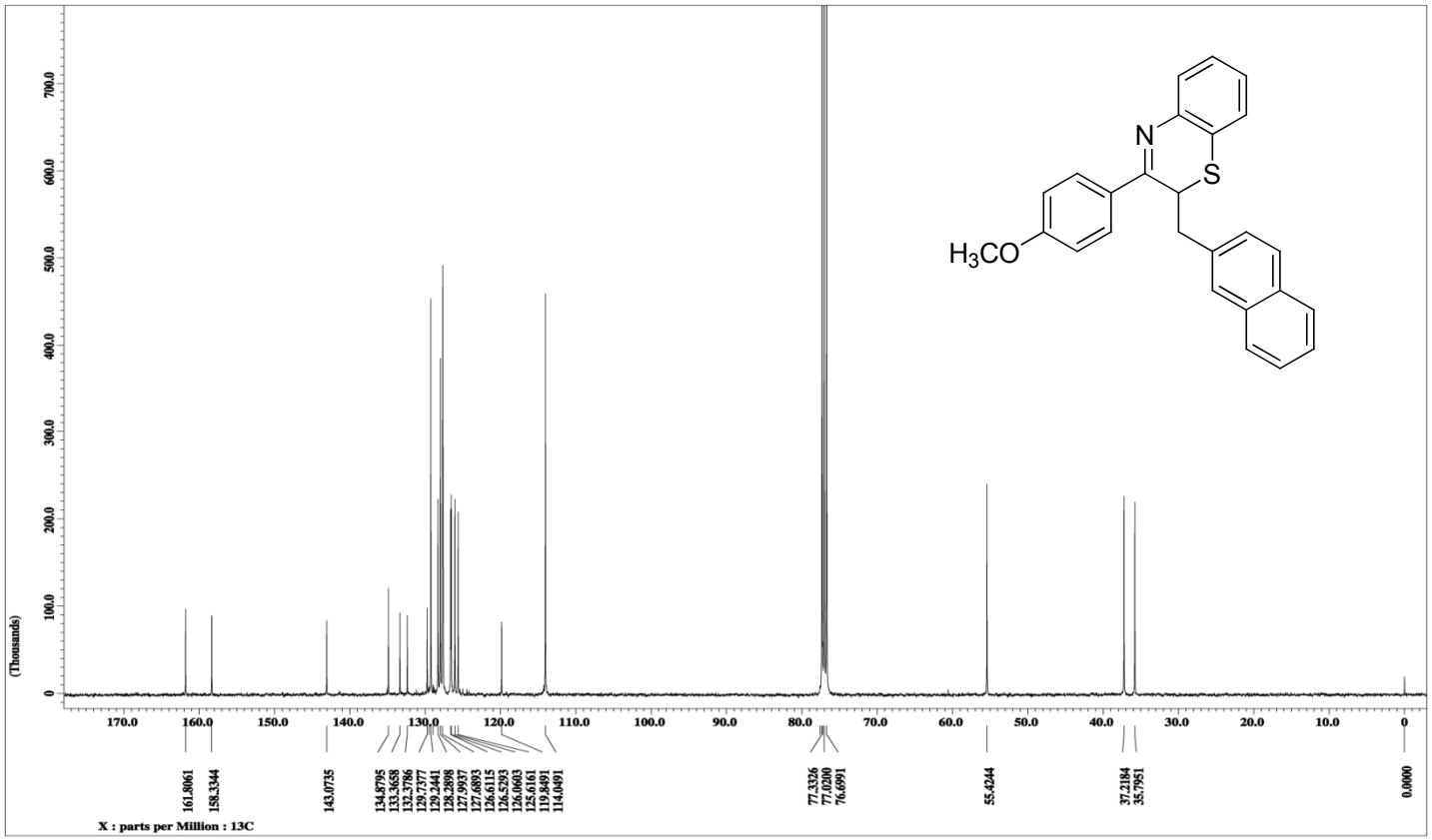
IR of 4-(2-(2, 4-dichlorophenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)aniline MA15



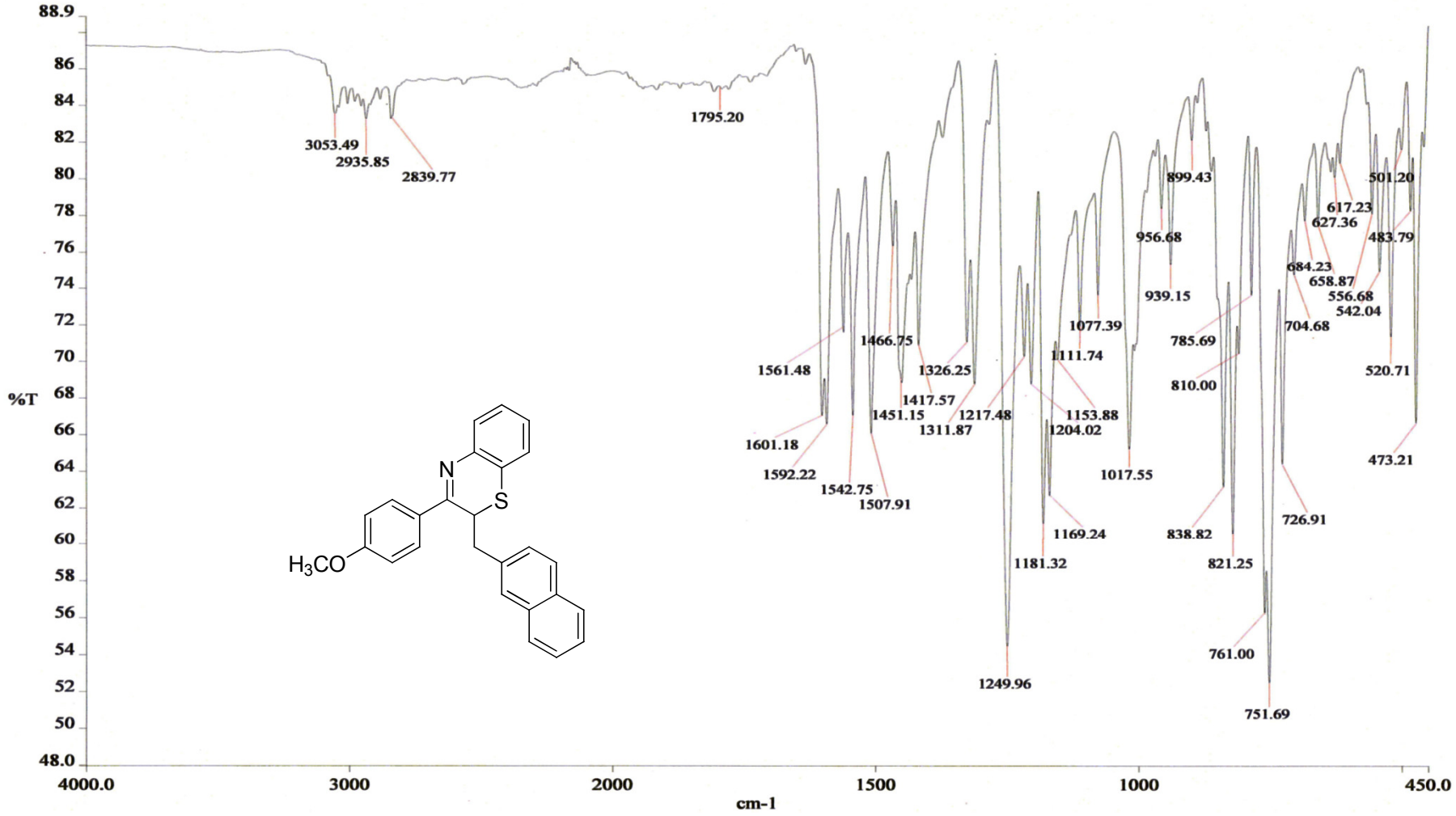
[1]HNMR of 3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine (6MR)



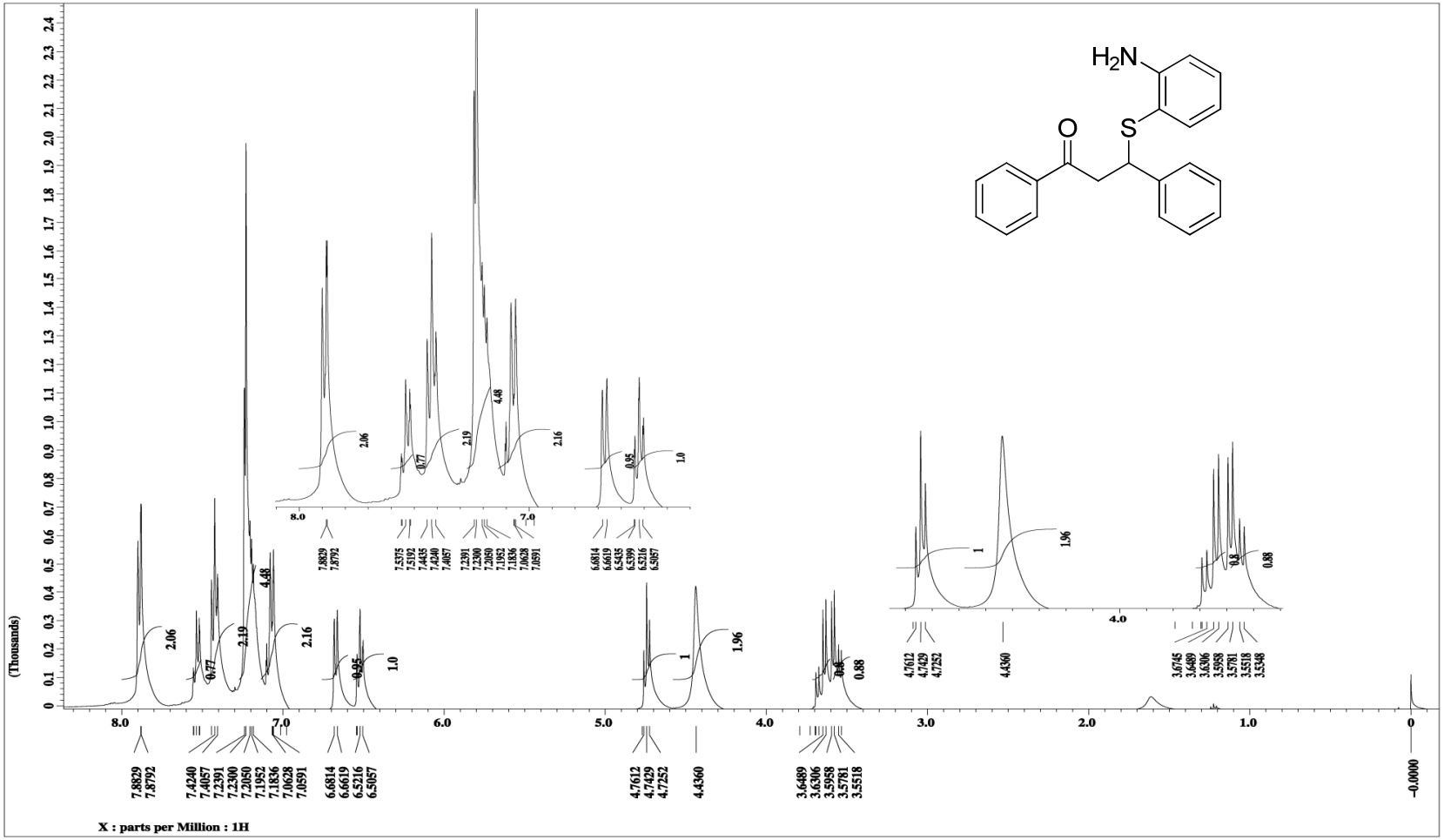
^{13}CNMR of 3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine (6MR)



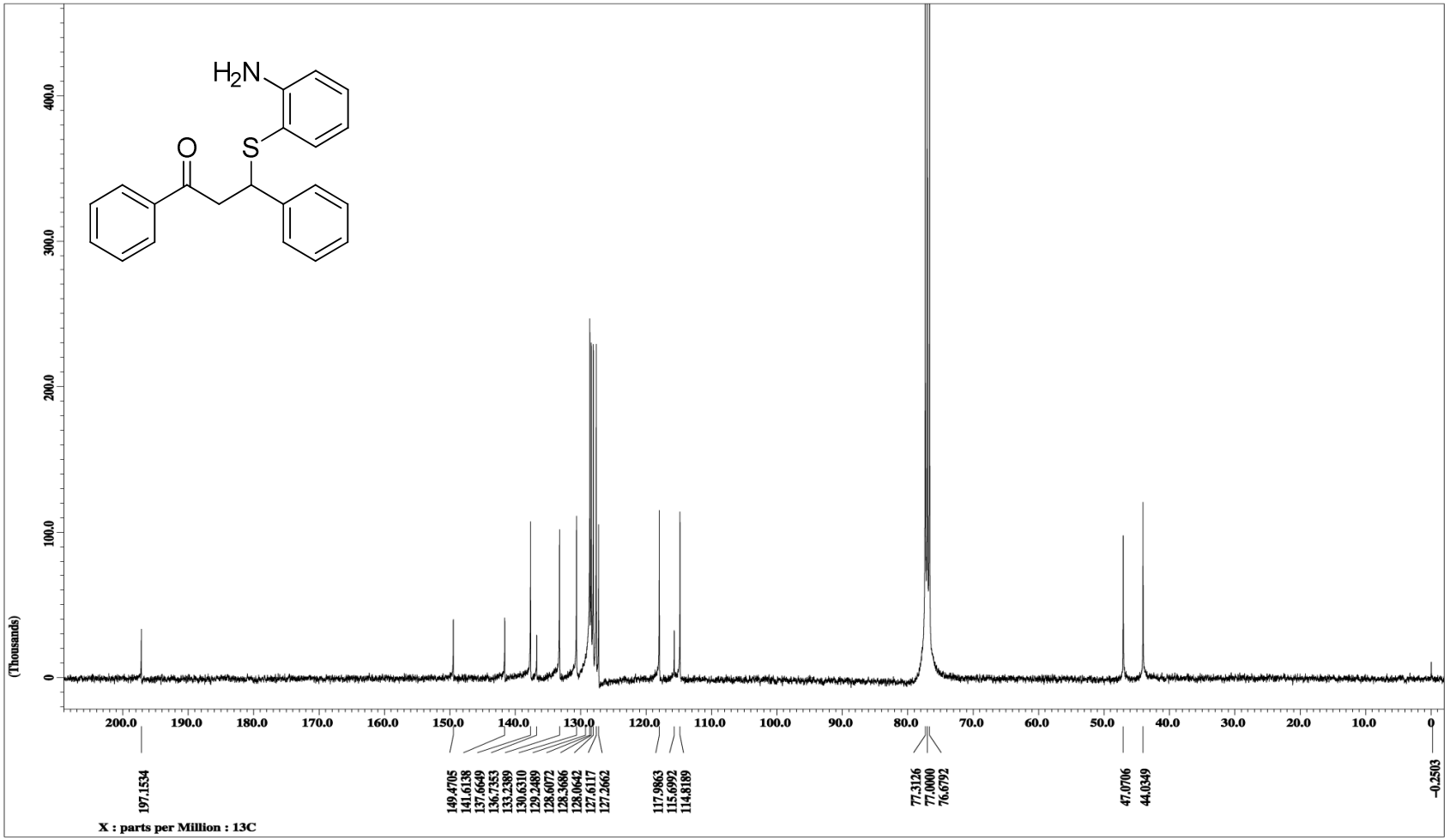
IR of 3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine (6MR)



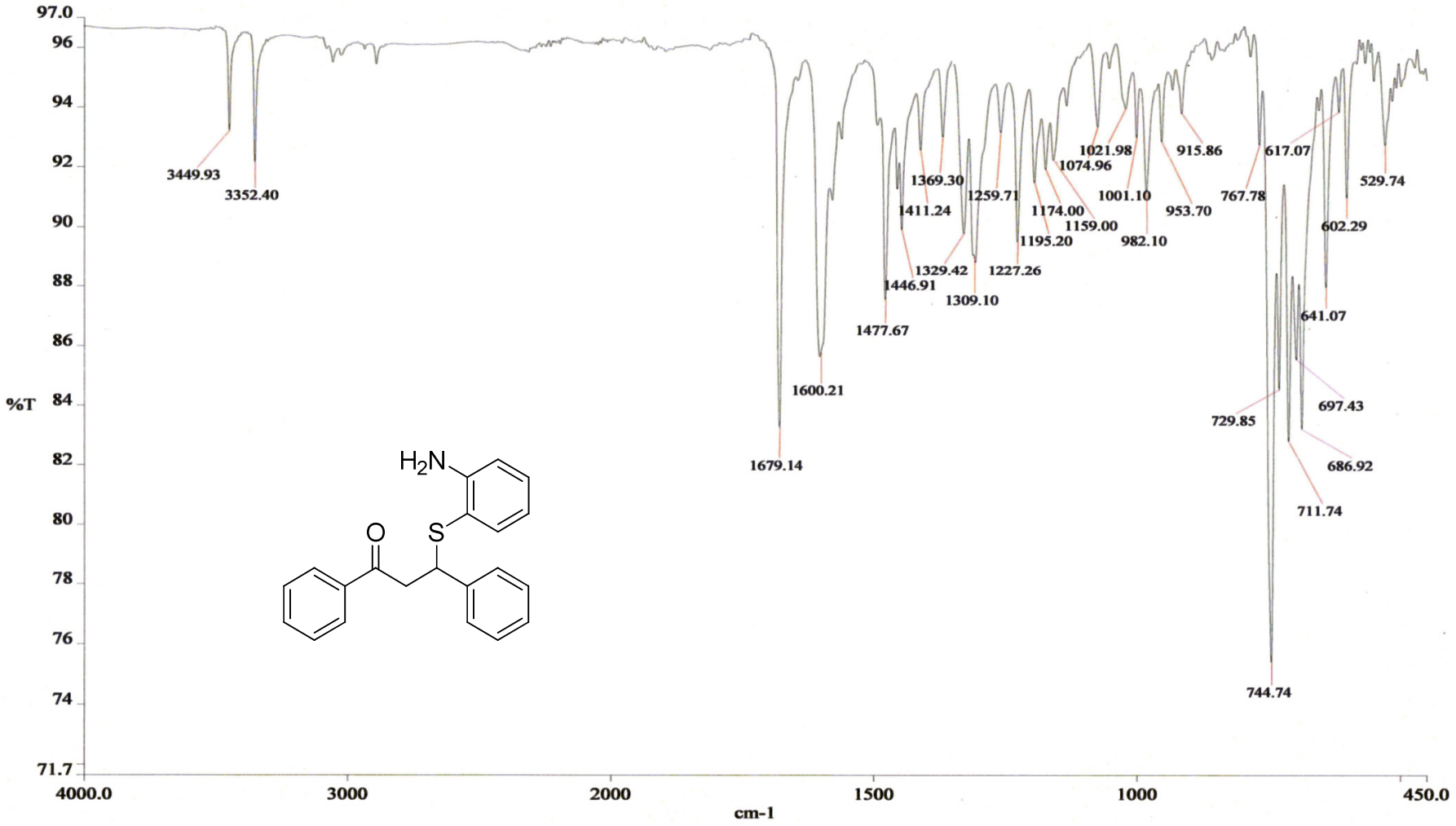
[1]HNMR of 3-(2-aminophenylthio)-1,3-diphenylpropan-1-one; Michael adduct



^{13}CNMR of 3-(2-aminophenylthio)-1,3-diphenylpropan-1-one; Michael adduct



IR of 3-(2-aminophenylthio)-1,3-diphenylpropan-1-one; Michael adduct

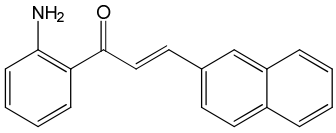


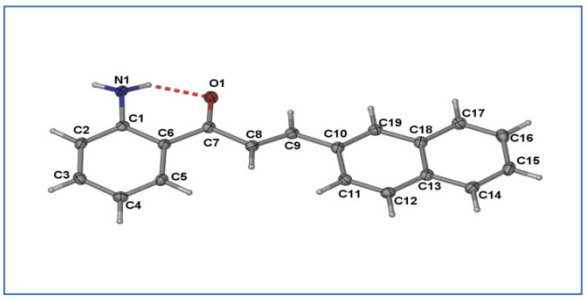
APPENDIX C

CRYSTAL DATA AND REFINEMENT DETAILS

X-ray diffraction data were collected on a Bruker APEX II CCD diffractometer using MoKa radiation. The structures were solved by direct methods and refined by a full-matrix least-squares procedure based on F^2

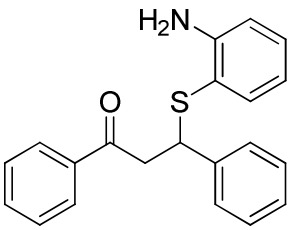
(*E*)-1-(2-aminophenyl)-3-(naphthalen-2-yl) prop-2-en-1-one MC42

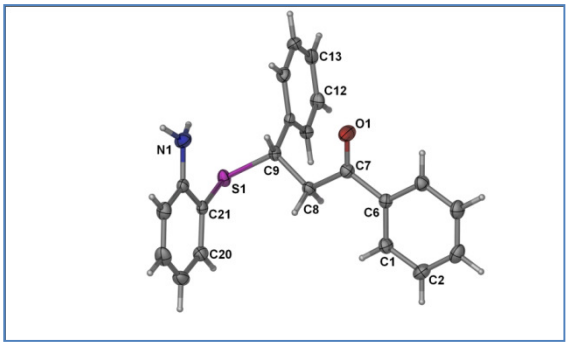




Empirical formula	C_{19} H_{15} N O
Formula weight	273.32
Crystal system	Monoclinic
Space group	P2(1)/n
a (Å)	13.595(3)
b (Å)	5.0500(10)
c (Å)	19.905(4)
α (°)	90
β (°)	98.593(2)
γ (°)	90
Volume (Å^3)	1351.2(5)
Z value	4
Calculated density, D_{calc} (Mg/m^3)	1.344
Crystal size (mm)	0.22 x 0.20 x 0.11
Crystal color and habit	yellow Blade
Reflections collected	7030
Independent reflections	2927 [R(int) = 0.0213]
Observed reflections (I > 2sigma(I))	2347
Completeness to theta = 26.99°	98.6 %
Final R indices [I>2σ(I)]	R1 = 0.0387, wR2 = 0.0942
R indices (all data)	R1 = 0.0387, wR2 = 0.0942

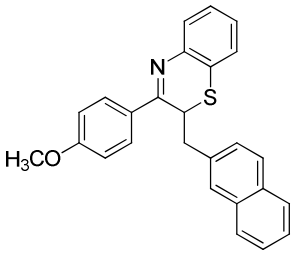
3-(2-aminophenylthio)-1,3-diphenylpropan-1-one **Michael adduct**

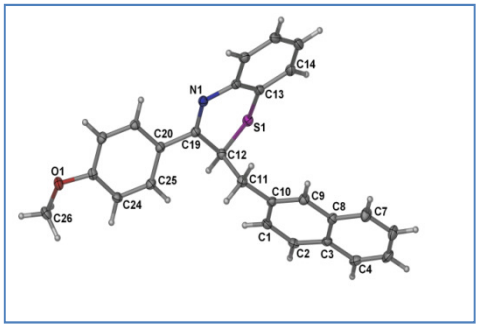




Empirical formula	C_{21} H_{19} N O S
Formula weight	333.43
Crystal system	Monoclinic
Space group	P2(1)/n
a (Å)	11.1741(16)
b (Å)	5.6788(8)
c (Å)	27.308(4)
α (°)	90
β (°)	95.266(2)
γ (°)	90
Volume (Å^3)	1725.5(4)
Z value	4
Calculated density, D_{calc} (Mg/m^3)	1.344
Crystal size (mm)	0.22 x 0.20 x 0.11
Crystal color and habit	Colorless, blade
Reflections collected	7303
Independent reflections	3195 [R(int) = 0.0648]
Observed reflections (I > 2sigma(I))	1784
Completeness to theta = 25.50°	99.7 %
Final R indices [I>2σ(I)]	R1 = 0.0568, wR2 = 0.0844
R indices (all data)	R1 = 0.1233, wR2 = 0.1008

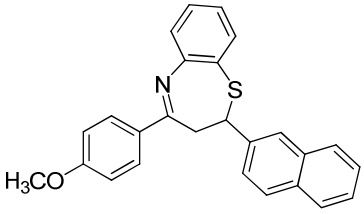
3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine 6MR

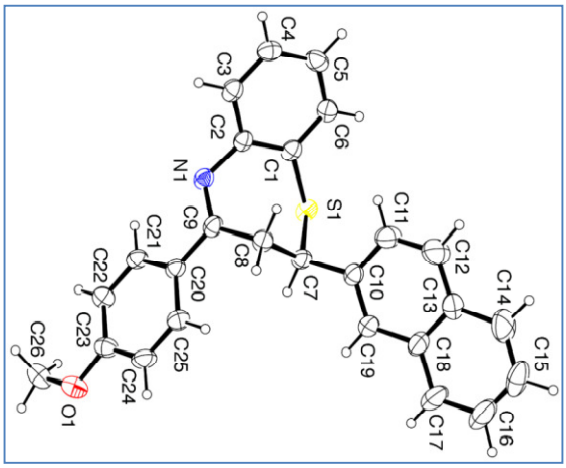




Empirical formula	$C_{26}H_{21}NOS$
Formula weight	395.50
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
a (Å)	8.9621(7)
b (Å)	12.2332(9)
c (Å)	18.2916(14)
α (°)	90
β (°)	90
γ (°)	90
Volume ($Å^3$)	2005.4(3)
Z value	4
Calculated density, D_{calc} (Mg/m^3)	1.310
Crystal size (mm)	0.30 x 0.20 x 0.10
Crystal color and habit	Yellow block
Reflections collected	24615
Independent reflections	4385 [R(int) = 0.0375]
Observed reflections (I > 2sigma(I))	4144
Completeness to theta = 27.00°	99.9 %
Final R indices [I>2σ(I)]	R1 = 0.0285, wR2 = 0.0691
R indices (all data)	R1 = 0.0314, wR2 = 0.0716
F(000)	832.00

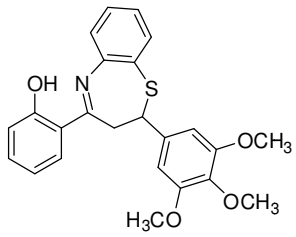
4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2, 3-dihydrobenzo[b][1,4]thiazepine
MA12

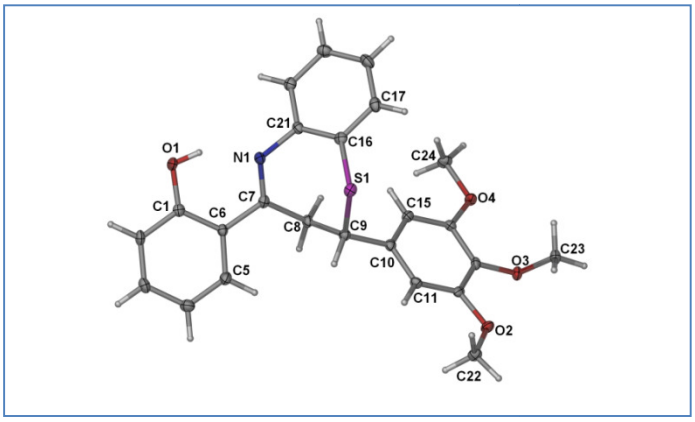




Empirical formula	$C_{26}H_{21}NOS$
Formula weight	395.51
Crystal system	Monoclinic
Space group	P b c a
a (Å)	18.821(2)
b (Å)	5.1632(6)
c (Å)	20.450(3)
α (°)	90
β (°)	94
γ (°)	90
Volume ($Å^3$)	1981.2(4)
Z value	4
Calculated density, D_{calc} (Mg/m^3)	1.323
Crystal size (mm)	0.30 x 0.08 x 0.06
Crystal color and habit	Pale yellow, columnar
Reflections collected	24615
Independent reflections	4385 [R(int) = 0.0375]
Observed reflections (I > 2sigma(I))	4144
Completeness to theta = 27.00°	99.9 %
Final R indices [I>2σ(I)]	R1 = 0.0285, wR2 = 0.0691
R indices (all data)	R1 = 0.0314, wR2 = 0.0716
F(000)	828.00

2-(2-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol
MA5





Empirical formula	C_{24} H_{23} N O_4 S
Formula weight	421.49
Crystal system	Orthorhombic
Space group	P b c a
a (Å)	10.6438(5)
b (Å)	13.6221(6)
c (Å)	27.4699(13)
α (°)	90
β (°)	90
γ (°)	90
Volume ($Å^3$)	3982.9(3)
Z value	8
Calculated density, D_{calc} (Mg/m^3)	1.406
Crystal size (mm)	0.30 x 0.08 x 0.06
Crystal color and habit	Yellow, bladed
Reflections collected	24294
Independent reflections	4352 [R(int) = 0.0732]
Observed reflections (I > 2sigma(I))	3150
Completeness to theta = 27.00°	99.9 %
Final R indices [I>2σ(I)]	R1 = 0.0419, wR2 = 0.0892
R indices (all data)	R1 = 0.0679, wR2 = 0.1006

LIST OF PUBLCATIONS

1. Synthesis of flavanones, azaflavanones and thioflavanones catalyzed by PMA/SiO_2 a mild, efficient and reusable catalyst. S.Raghavendra, **Marzieh Yaeghoobi**, **Noorsaadah Abd.Rahman.** *Monatshefte fur chemie. (2011).143, 797-800* (ISI/Scopus cited Publication)

2. (E)-3-(6-Nitrobenzo[d][1,3]dioxol-5-yl)-1-(2,4,6-trimethoxyphenyl) prop-2-en-1-one . Hossein Loghmani-Khouzani, **Noorsaadah Abdul Rahman**, Ward T Robinson, **Marzieh Yaeghoobi** and Reza Kia. *Acta Cryst. (2009). E65, o2545*(ISI/Scopus cited Publication)

3. 3-(2-Aminophenylsulfanyl)-1,3-diphenylpropan-1-one. **Marzieh Yaeghoobi**, Hamid Khaledi, **Zanariah Abdullah** and **Noorsaadah Abd.Rahman.** *Acta Cryst. (2011). E67, o1693* (ISI/Scopus cited Publication)

4. 4-Chloro-2-[(*E*)-2-(4-methoxyphenyl)-ethyliminomethyl] phenol. **Marzieh Yaeghoobi**, **Noorsaadah Abd. Rahman** and Seik Weng Ng. *Acta Cryst. (2009). E65, o1070* (ISI/Scopus cited Publication)

5. An efficient synthesis of 1, 5-Benzothiazepines in germinal dicationic Ionic liquids. **Marzieh Yaeghoobi**, Raghavendra Sakirolla, Zanariah Abdullah, Hossein Loghmani- Khouzani, Puvaneswary Subramaniam, Yatimah Alias, **Noorsaadah Abd.Rahman.** (*Submitted to Monatshefte fur chemie)*

6. QSAR Studies on Chalcone Derivatives as New Potential Inhibitors for H1N1 Virus Neuraminidase. **Marzieh Yaeghoobi**, Neni Frimayanti, N. Kusaira K. Ikram , Sharifuddin M. Zain, **Zanariah Abdullah**, Habibah A. Wahab, and **Noorsaadah Abd. Rahman**.(*Submitted to Bioorganic &Medicinal Chemistry Letters)*

7. Docking, Synthesis and Bioassay Study of Imine Derivative as Potential Inhibitor NS2B/3 Serine Protease for Dengue. Neni Frimayanti, **Marzieh Yaeghoobi**, Heh Choon Han, Sharifuddin M. Zain, Rozana Othman, Rohana Yusof, and **Noorsaadah Abd. Rahman**.(*Submitted to Bioorganic &Medicinal Chemistry Letters)*

8. Efficient and Eco-friendly Syntheses of 1,5-Benzothiazepines and 1,5-Benzodiazepines Catalyzed by [*Hmim*][NO_3]Under Mild Conditions. Panteha Tamjidi, Hossein Loghmani-Khouzani, Iraj Mohammadpoor-Baltork, **Marzieh Yaeghoobi**, **Noorsaadah Abd.Rahman**, Ahmad Reza Khosropour, Majid Moghadam, Shahram Tangestaninejad, Valiolah Mirkhani, Mohammad Hossein Habibi, Ayana Kashima, Takayoshi Suzuki. .(*Accepted in journal of Heterocyclice Chemistry)*

Presentations at the following conferences:

1. **Marzieh Yaeghoobi, Noorsaadah Abd. Rahman.** "STUDY TOWARDS SYNTHESIS OF PDT COMPOUND", 6th Singapore International Chemical Conference (SICC 6). Singapore. Dec 2009
2. **Marzieh Yaeghoobi,** Raghavendra Sakirolla, **Noorsaadah Abd. Rahman.** "PMA-SiO_2, AN EFFICIENT CATALYST FOR FLVANONE SYNTHESIS", University of Malaya-Hyderaad University bilateral seminar, UM, Malaysia. Oct 2010
3. **Marzieh Yaeghoobi**, **Noorsaadah Abd. Rahman, Zanariah Abdullah.** "IONIC LQUID PROMOTED AZEPINE SYNTHESIS", 14^{th} Asian Chemical Congress, Bangkok, Thailand. Sep 2011
4. **Marzieh Yaeghoobi,** Raghavendra Sakirolla, **Noorsaadah Abd. Rahman.** "DICATIONIC IONIC LQUID PROMOTING AZEPINE SYNTHESIS", NaSOS II, UiTM, Malaysia,. June 2012