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# Multicomponent Reactions for the Preparation of Fluorous Taged Pyrimidines and Thiopyrimidines and their Derivatisation to Obtain Biaryl-Substituted Heterocycles

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# MULTICOMPONENT REACTIONS FOR THE PREPARATION OF FLUOROUS TAGED PYRIMIDINES AND THIOPYRIMIDINES AND THEIR DERIVATISATION TO OBTAIN BIARYL-SUBSTITUTED HETEROCYCLES

A Thesis Presented

by

BRUNO PIQANI

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ABSTRACT

MULTICOMPONENT REACTIONS FOR THE PREPARATION OF FLUOROUS TAGED PYRIMIDINES AND THIOPYRIMIDINES AND THEIR DERIVATISATION TO OBTAIN BIARYL-SUBSTITUTED HETEROCYCLES

December 2011

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Directed by Professor Wei Zhang

This thesis presents a work in the field of multicomponent reactions (MCRs), one-step condensation between a fluorous tagged aldehyde, *β*-keto ester and urea derivatives. This process in literature is known as "Biginelli Reaction". This dissertation describes a new Biginelli reaction element, using fluorous component as a limiting agent.

Chapter one is an introduction of MCRs. A brief historical review, key principles as well as applications in different fields such as academic research, synthetic organic chemistry, and medicinal applications are presented.

Chapter two discusses the general features of the Biginelli reaction, microwave, and fluorous chemistry with a distinctive look from the perspective of green chemistry.

In chapter three our efforts in expanding the procedures to new fluorous components such as fluorous tagged DHMPs are examined. Interesting features for the synthetic process were reveled through multiple types of reagents-controlled synthesis. Suzuki reaction with phenyl boronic acids is explored. The extent of the different structures and the stereochemical preference are discussed. The possibility of Suzuki coupling of thiazolopyrimidine structures by conducting a cycloaddition reaction was investigated. A five member ring was added to the position 2 and 3 of the dihydropyrimidine scaffold to obtain 5*H*-Thiazolo 2,3 pyrimidines. Two analogues from cycloaddition reaction were obtained for Suzuki couplings to afford eight final products.

Another feature that we were able to explore was the synthetic manipulation of thiazolopyrimidine adduct obtained from the Biginelli reaction. The reactivity of the double bonded sulfur toward palladium promoted transformations allowed for the synthesis of various heterocycles through Liebeskind-Srogl desulfative coupling followed by Suzuki cross-coupling reactions.

# DEDICATION

*To my wife Anila and my children Clarissa and Edward.*

ACKNOWLEDGEMENTS

The entire work presented in this thesis is the result of investigations carried out by me from September 2008 to May 2011 at the Department of Chemistry at UMass Boston under the supervision of Prof. Dr. Wei Zhang.

I would like especially to thank Prof. Wei Zhang who has given me the opportunity to carry out my study in his research group and to explore myself by working in the fascinating field of fluorous chemistry. I am deeply indebted to him for his inspiring guidance, constant encouragement, helpful discussion and giving me a lot of freedom and enthusiasm in doing different kinds of reactions. His guidance and supervision was really stimulating and helped me broaden my scientific horizons in directions I had not imagined.

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LIST OF ABBREVIATIONS

| | |
|---|---|
| **DEAD** | Diethyl azodicarboxylate |
| **DHPM** | Dihydropyrimidine |
| **DMF** | Dimethylformamide |
| **DMSO** | Dimethyl sulfoxide |
| **F-SPE** | Fluorous Solid-Phase Extraction |
| **LC-MS** | Liquid chromatography-mass spectrometer |
| **MAOS** | Microwave-assisted organic synthesis |
| **MCR** | Multicomponent reaction |
| **MW** | Microwave |
| **NMR** | Nuclear magnetic resonance |
| **TBAB** | Tetrabucylammonium bromide |
| **TBAF** | Tetrabutylammonium fluoride |
| **TFA** | Trifluoroacetic acid |
| **TFP** | Tetrafluoropropanol |
| **THF** | Tetrahydrofuran |
| **TLC** | Thin layer chromatography |
| **TPP** | Thiamine pyrophosphate |

# CHAPTER 1

# GENERAL ASPECTS AND HISTORIC DEVELOPMENT

## 1.1. Multicomponent Reactions (MCRs).

MCRs are one-pot processes that combine three or more substrates simultaneously.[1] Such processes are of great interest, not only because for their application in diversity-oriented synthesis to generate compounds for screening purposes, but also of their green chemistry features, such as the atom economy, solvent free synthesis or synthesis in water.[2]

The outcome of MCRs depends on the nature of the reactants as well as the reaction conditions (solvent, temperature concentration etc).[3] For a MCR to be feasible and efficient in principle, the compatibility, as well as the relative reactivity of all reagents is to be considered during the planning stages. This is of great importance since these processes constitute a network of elementary reactions between the different components.[4]

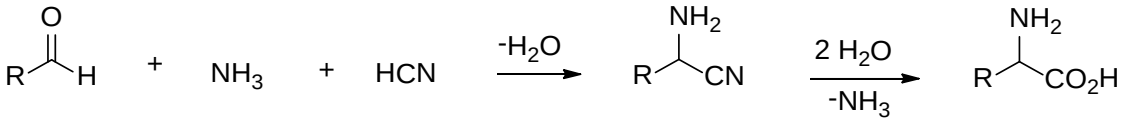
Multiple equilibrium coexist with reactive species which are formed in-situ and then participate in an irreversible step that drives the reaction toward the final product, thus making the process efficient and free of byproducts.[5]

MCRs are valuable reactions because they combine characteristics such as: improved yields compared with the linear multistep reactions, atom economy, and shorter (one-pot) synthetic routes, access to a large number of products and high exploratory power.[6] The number of products increases with the multiplicity of the reaction and also by changing the structure of the starting materials.

These characteristic used in combination with the high degree of functionality can be exploited for the construction of a large number of products for biological screening, in drug design, as well as in structure-activity relationship studies of biologically active compounds, extending the importance of MCRs to the fields of biology, medicinal chemistry and drug research and development.[7]

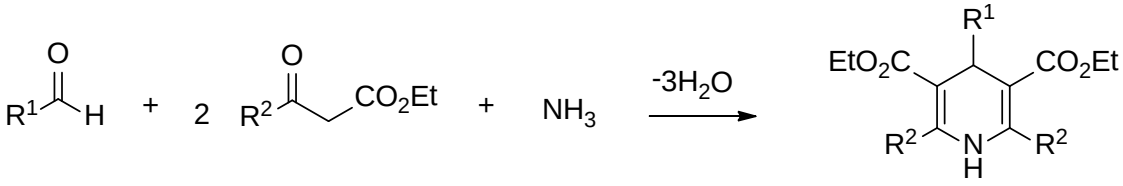
As a result, in recent years the number of articles published in the field shows that the trend is increasing.[8] Research and development in the field of MCRs will continue to be very active. The intellectual challenge in developing new and efficient MCRs based on the knowledge accomplished so far, together with the need for small, easily accessible drug-like compounds are behind the challenges that make this field one of the most interesting areas of organic chemistry.

In 1850, a contribution to the development of MCRs was made by A. Strecker.[9] Strecker reaction is a three component reaction of an aldehyde or ketone with ammonia and hydrogen cyanide to give α-aminonitriles. The reaction belongs in the category of deoxo-bisubstitution reaction of aldehydes. Subsequent hydrolysis of α-aminonitriles gives as a result α-amino acids (Scheme 1).



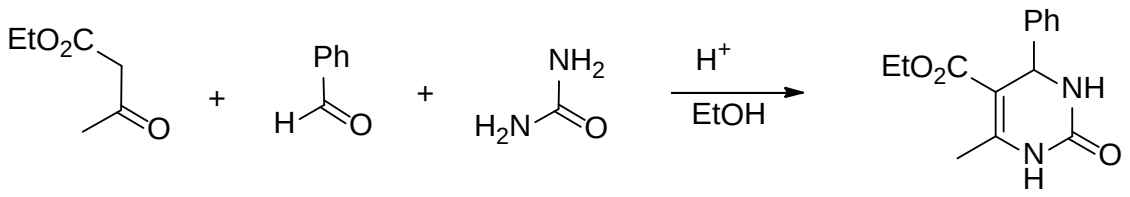

Scheme 1. Strecker synthesis of α-amino acids

Second example of multicomponent reaction came from the work of Hantzsch in 1881.[10] The classical form of this reaction involves the formation of dihydropyridines from an aldehyde a *β*-ketoesther and an amine (Scheme 2). The reaction belongs in the category of carbaacetalization reaction of aldehydes.



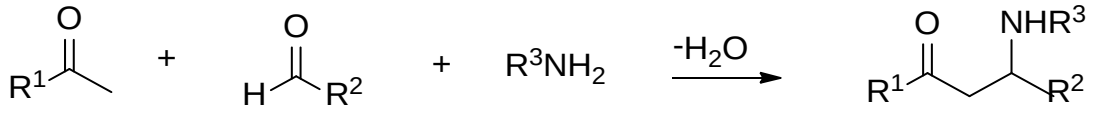

Scheme 2. Hantzsch multicomponent synthesis of dihydropyridines

The Biginelli reaction, first described in 1893, represents a multicomponent synthesis of acetoacetate, benzaldehyde and urea in ethanol (Scheme 3).[11] This reaction like the Strecker reaction is a deoxo-bisubstitution reaction of aldehydes.



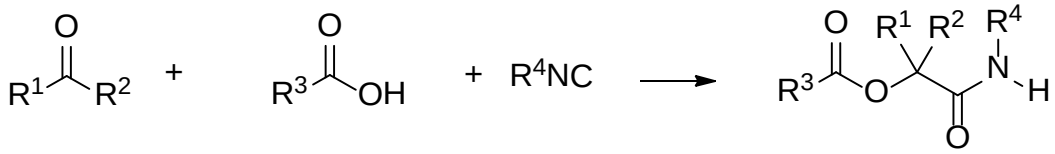

Scheme 3. Biginelli multicomponent synthesis of dihydropyrimidine

Back in 1912, C. Mannich reported a three-component reaction that involves the nucleophilic addition of an enol to an iminium ion formed by the reaction of formaldehyde with a secondary amine to produce β-amino carbonyl compounds (Scheme 4).[12]



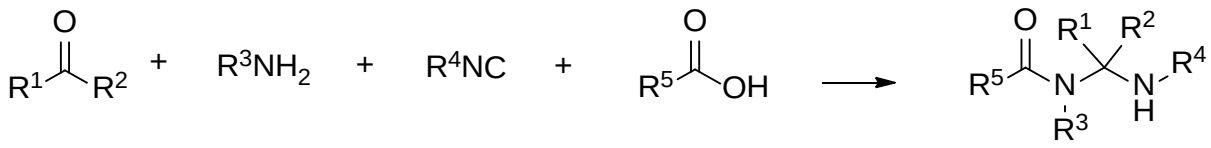

Scheme 4. Three-component Mannich reaction

The first MCR using isocyanides was reported by Passerini in 1921. The Passerini reaction is a one-pot condensation reaction between a carboxylic acid, a carbonyl compound and an isocyanide. The formed product is a *α*-acyloxycarboxamide derivative (Scheme 5).[13] This reaction could be described as an addition reaction to aldehydes where a C−C is formed and the C=O of an aldehyde is converted to a C−O bond.




Scheme 5. Passerini's three-component reaction

One multicomponent reaction with a tremendous importance was reported in 1962 by Ivar Ugi.[14] Synthesis of α-acylamido amide was attained in a four-component reaction of ketone or aldehyde, an amine, an isocyanide and a carboxylic acid (Scheme 6.). This is another example of a deoxo-bisubstitution reaction of aldehydes.




Scheme 6**.** Ugi four-component reaction

Described above are the most popular multicomponent reactions. MCR chemistry has been proven to have advantages in terms of diversity and efficiency, which can be utilized in technological and scientific advancements.[15]

# CHAPTER 2

# LITERATURE REVIEW

## 2.1. Green Chemistry

During the past century chemistry has changed the way we live. These changes came with a price, such as environmental pollution and the earth has been subjected to it since the beginning of the industrial revolution.[16] As a consequence of the pollution, plant and animal extinction has worsened in the past decades.[17]

Water pollution has resulted in the depletion of both fresh water and ocean fish stock, thus leaving less of these resources for human consumption.[18] Emission of greenhouse gases potentially can also result in massive extinction of plant and animal lives due to global warming.[19] As early as the 1990s, a new concept was introduced in the chemistry language known as green (sustainable) chemistry.[20] Green and sustainable chemistry is largely concerned with the development of processes and technologies that result in efficient chemical reactions that generate[21] less waste and less environmental emissions. Thus, instead of limiting risk by controlling our exposure to hazardous chemicals, green chemistry attempts to reduce and preferentially eliminate these

hazards.[22] There are twelve principles of green chemistry that have been set down by Anastas and Warner: [23]

1. Waste prevention
2. Atom economy
3. Less hazardous chemical synthesis
4. Designing safer chemicals
5. Safer solvents and auxiliaries
6. Design for energy efficiency
7. Use of renewable feedstock
8. Reduce derivatives
9. Catalysis
10. Design for degradation
11. Real-time analysis for pollution prevention
12. Inherently safer chemistry for accident prevention

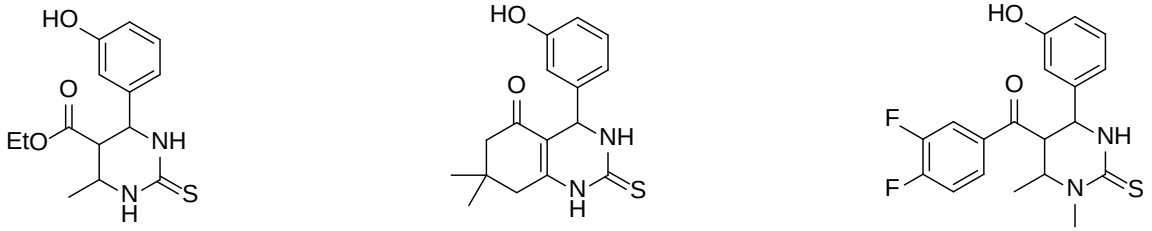
Chemistry, as a central science, is one of the keys on finding ways to handle green and sustainable ways for environmentally friendly advancement.[24] Green chemistry is an integrated study in the chemical, biological, physical and engineering fields. Nevertheless even research in materials science that includes nanomaterials[25] and rigid materials[26] can be approached using green chemistry principles.

Aspects of green chemistry that are considered in this research are combination of synthetic routes that use MCRs, microwave, fluorous tags and in few examples, the use of water as a solvent. This thesis includes few approaches and findings, intentionally directed toward green chemistry. Main focus in this study will be placed on examples from organic chemistry, specifically on catalyzed reactions. In particular, the study deals with fluorous compounds for the easiness of their separation.

## 2.2. The Biginelli Reaction

The Biginelli reaction was first carried out by refluxing a mixture of an aldehyde, *β*-keto ester, and urea dissolved in ethanol with a small amount of HCl at reflux temperature. The product was obtained by precipitation after cooling of the reaction mixture and was identified as 3,4-dihydropyrimidin-2(1*H*)-one (Scheme 3). This one-pot, three-component condensation reaction is called the “Biginelli reaction”, “Biginelli condensation”, or “Biginelli DHPM synthesis”. It was first reported by Pietro Biginelli in 1893.[11]

DHPMs generated from this reaction are compounds with pharmacological, antiviral and antibacterial activities also calcium channel modulators and mitotic kinesin Eg5 inhibitors **1-3**.[27] Human kinesin Eg5 plays an essential role in cell mitosis, and could be an attractive drug target for the development of cancer chemotherapeutics.[28]




**1** **2** **3**

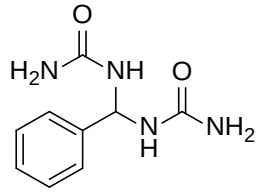
Enastrol Dimethylenastrol Fluorastrol

Figure 1. Human kinesin Eg5 inhibitors

The original Biginelli reactions were obtained with low yields and were limited in scope. Since the discovery of the biological activity of DHPM derivatives the Biginelli

reaction has received renewed interest. The latest developments have provided a plethora of different reaction conditions, a variety of compatible solvents, quite a few catalysts, and an extended substrate range.[29] Most recently, the development of more stereoselective methods has allowed the generation of enantiomerically enriched compounds.[30]

Since the Biginelli reaction was first reported, there have been several attempts to explain its mechanism. The first attempts were made by Folkers and Johnson in 1930. According to them the mechanism of the Biginelli reaction was a series of bimolecular reactions leading to the desired dihydropyrimidinone.[31] They reported that one of the three intermediates **4-6** could be formed during the reaction.

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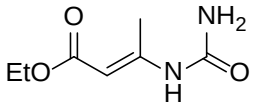


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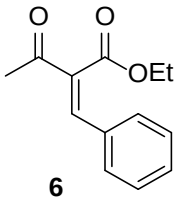
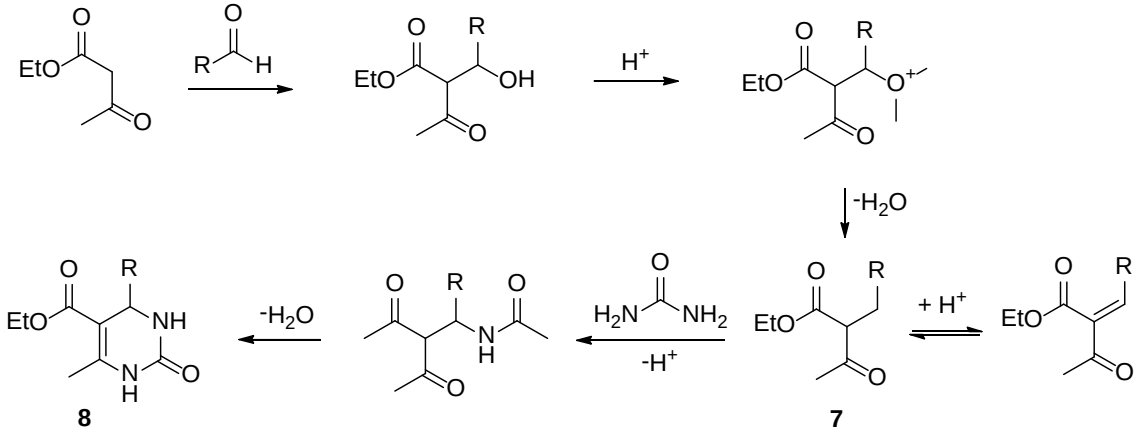



**6**

Figure 2. Intermediates proposed by Folkers and Johnson for the Biginelli reaction

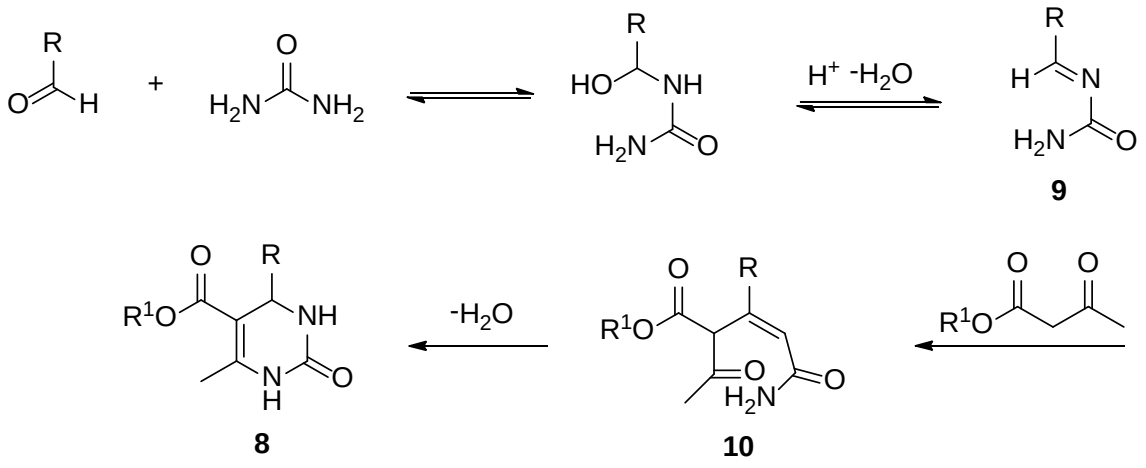
*N*,*N*-benzylidenebisurea **4** forms from the condensation of benzaldehyde with two molecules of urea. 3-ureido ethyl acrylate intermediate **5** is formed by condensation of *β*-ketoesther and urea, whereas intermediate **6** is an aldol adduct formed as in the Knoevenagel condensation.[32] In 1973, Sweet and Fissekis[33] proposed a new mechanistic interpretation for the Biginelli reaction. This mechanism is based on the formation of a stabilized carbenium ion **7** in the rate-limiting step of an acid-catalyzed aldol

condensation between benzaldeyde and ethyl acetoacetate. Carbenium ion can react with urea which dehydrates to give the desired product **8** (Scheme 7).




Scheme 7. Sweet and Fissekis mechanistic proposal

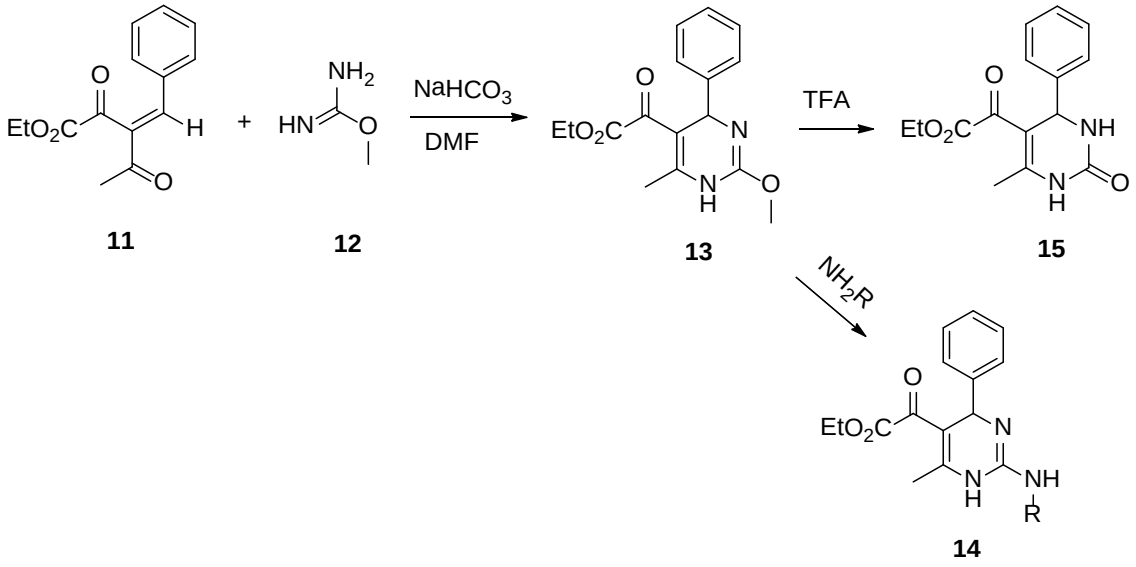
In 1997 Kappe suggested that rate determining step is nucleophilic addition by the urea to the aldehyde.[34] The subsequent condensation, results in the imine nitrogen **9**. The *β*-ketoester adjoins the imine bond and the nucleophilic addition by the amine to the carbonyl, closes the ring **10**. A second condensation follows the final step producing the Biginelli compound **8** (Scheme 8).




Scheme 8. Kappe's mechanistic proposals for the Biginelli reaction

For many years the “Achilles heel” for the Biginelli reaction was the low and variable yields and limited scope.[35] Nowadays with a plethora of information regarding its mechanism, several advancements were made to address the problem. Hu and coworkers reported that the application of $BF_3 \cdot OEt_2$, gave substantial yield increase when an one-pot reaction in acetic acid and THF was run with $Cu(OAc)_2$.[36] Also Kappe and Falsone reported that polyphosphate ester in THF gives increased reaction yields.[37]

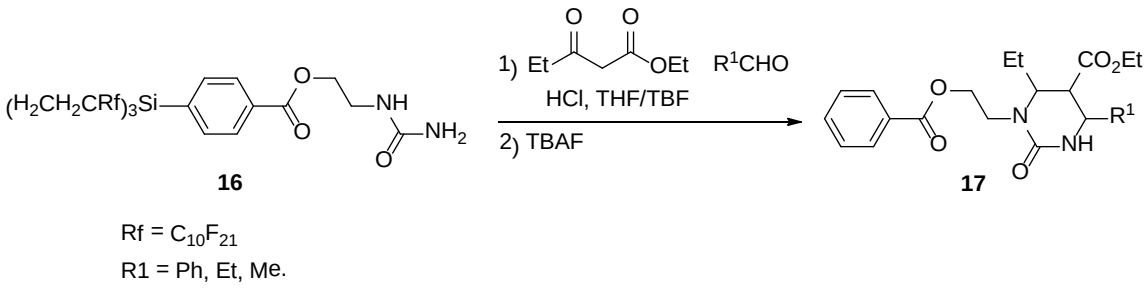
Atwal and coworkers modified the original Biginelli condensation which can provide high product yields and the preparation of new dihydropyrimidines[38] (Scheme 9). This modification involves reaction of unsaturated keto-esters **11** with a protected urea derivative **12** to give a 2-substituted dihydropyrimidine **13**. Deprotection with trifluoroacetic acid (TFA) yields the dihydropyrimidine product **14**, at the same time deprotection with ammonia derivatives gives novel amino pyrimidines **15**.




Scheme 9**.** Atwal modification

The diverse biological activity of dihydropyrimidines is the foundation of their therapeutic potential.[27] To look at this activity, libraries of dihydropyrimidines have been created using microwave, solid-phase, and fluorous technologies.[39] Kappe and Stadler describe the automated microwave reaction to form dihydropyrimidines.[40] A variety of forty eight compound libraries were prepared within twelve hours.

Fluorous chemistry can be used for the synthesis of dihydropyrimidines. Curran and coworkers have reported methods based on the ability for highly fluorinated compounds to separate into a fluorinated solvent.[41] Fluorous ureas **16**, were used for the Biginelli reaction. The products were extracted into fluorinated hexanes (Scheme 10). Desilylation produces substituted dihydropyrimidines **17**. The yields for the fluorous reactions are similar to reactions performed under standard Biginelli reaction conditions.




Scheme 10. Fluorous Biginelli reaction

The advances of Biginelli condensation reaction are significant since its discovery 118 years ago. Advancements in science have provided modifications to methods, allowing high yields, in building novel dihydropyrimidine scaffolds. The diverse biological activity of dihydropyrimidines has been surveyed through the generation of libraries of compounds via MCRs, microwave, solid-phase, and fluorous technologies. The front line of the Biginelli condensation will continue to be developed as new methods are being reported and as new features of this class of compounds will be discovered in the future.

## 2.3. Fluorous Chemistry

The fluorous approach to the synthesis of small organic molecules provides an alternative to traditional solution and solid phase synthesis. Fluorous molecules contain an organic domain and a highly fluorinated (fluoroalkyl) domain.[42] organic domain controls reactivity and the fluorinated domain controls separation.

A brief history of fluorous chemistry is described below: [43]

1991 Thesis by Vogt (Univ. of Aachen) on the use of perfluorinated ethers to immobilize homogeneous catalysts.

1993 Zhu (3M) reported on azeotropic separations using perfluorocarbon solvents.

1994 Horváth & Rabai in *Science* described the use of heavily-fluorinated compounds in fluorous solvents for hydroformulation of biphasic catalysis. For the first time term "fluorous" was introduced.

1999 Curran (Univ. of Pittsburgh) develops "light" fluorous chemistry. The less-fluorinated compounds were soluble in organic and hybrid solvents, making fluorous techniques more practical in organic synthesis.

2000 Fluorous Technologies, Inc. founded to commercialize light fluorous chemistry.

2004 Peters and coworkers (Novartis) report use of fluorous tags for protein enrichment in proteomics applications.

The difference in the percentage by weight of fluorine on a fluorous material makes the difference between "heavy" and "light" fluorous chemistry. Generally, more than 60% fluorine materials have limited solubility in non-fluorous media. They typically

require perfluorinated solvents, and form a distinct liquid phase. This ability can be utilized for liquid-liquid separations, although reactivity is limited to the phase interface.[44]

"Light fluorous" compounds (less than 40% by weight) on the other side are usually soluble in organic solvents and cost less. Since they typically contain a single perfluorooctyl group, they will not form a separate fluorous liquid phase.[45] The basic mechanism of separation is fluorine-fluorine affinity. A fluorous sorbent is a chromatographic packing material modified with a highly fluorinated domain (Figure 3).

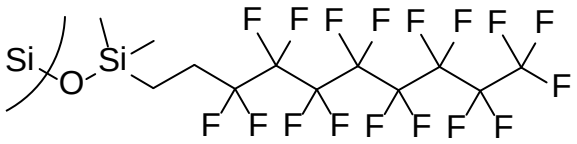
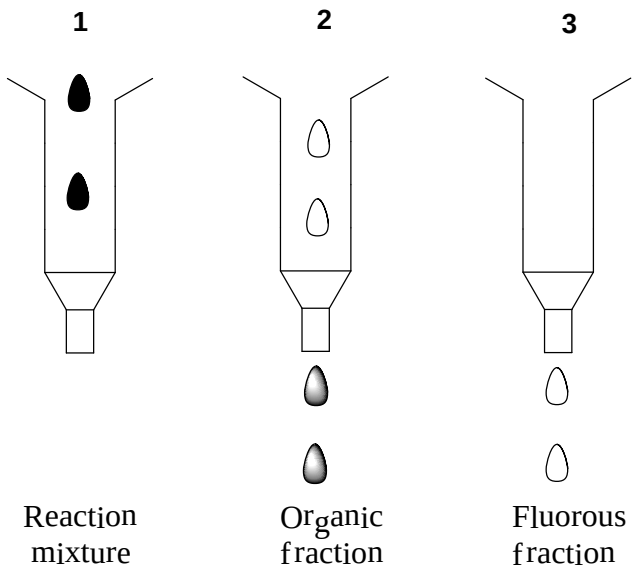



Figure 3. Fluorocarbon bonded phase packing material

Fluorous stationary phases exhibit high selectivity for retention of fluorous molecules. In addition, fluorous sorbents are able to resolve fluorous molecules with different fluorine content (different number of fluorous tags).[46] The $C_8F_{17}$ bonded phase shown above (Figure 3) is commercially available and is the most commonly used material for florous solid-phase extraction (F-SPE) technique.[47]



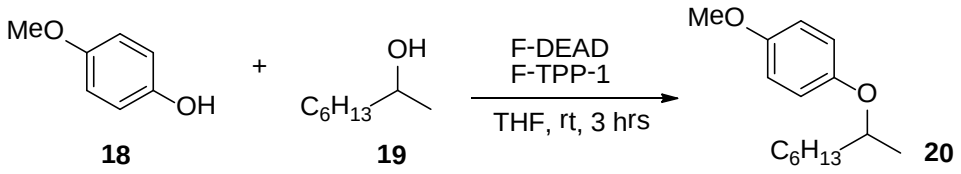

1. Load sample
2. Fluorophobic wash with MeOH-$H_2O$ *(80:20)* to remove organic species
3. Fluorophilic wash with THF, Acetone to elute fluorous species

Figure 4. Typical procedure for separating fluorous-tagged compounds from an organic reaction mixture

In fluorous phase extractions relatively high loadings of substrate/silica are used, and all of the fluorous components in the mixture behave identically and are collected in the same fraction, contrary to the conventional chromatography onlu two fractions (florous and non fluorous) are collected.[43]

Examples of reactions that use fluorous reagents to promote the transformation of a small molecule substrate into a product are described below:

The Mitsunobu reaction is the most efficient method for direct substitution of alcohols.[48] This is a reaction between a phenol **18** and a secondary alcohol **19** and is promoted by an azodicarboxylate (DEAD) and triphenylphosphine (TPP). Separation of the products and reagents is often problematic.[49] In 2002 Dandapani and Curran[50] reported the use of fluorous-labeled DEAD and TPP for easy separation by F-SPE (Scheme 11).




F-DEAD = $C_6F_{13}(CH_2)_3O_2CN$
F-TPP-1 = 4-$[C_8F_{17}(CH_2)_2]C_6H_4P(C_6H_5)_2$

55% yield
96% purity (GC)

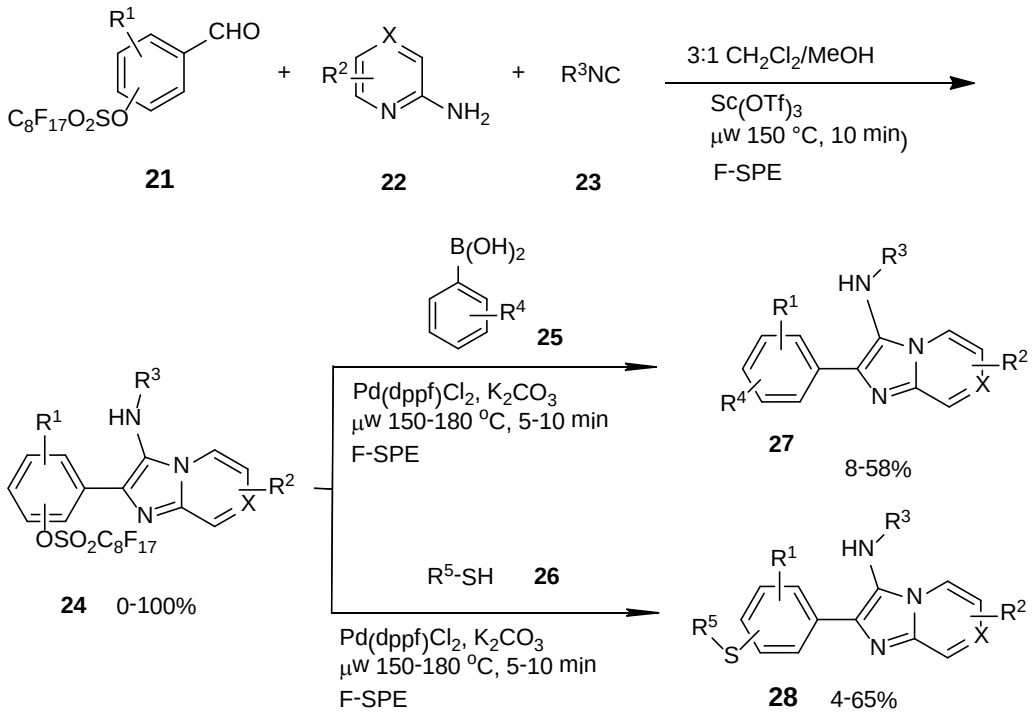
Scheme 11. Light Fluorous Mitsunobu Reaction

The use of a key fluorous component as limiting reagent in a MCR allows for quick isolation of the tagged product away from the complex mixtures containing reagents and by-products. After the MCR is completed, the tag is replaced by another element in a phase switch that provides further purification for removing unwanted products.[51]

Fluorous reactions can be easily monitored by analytical methods such as TLC, LC-MS, IR, and NMR since the fluorous molecules have defined molecular weights and structures.[52] In addition, the reaction and analytical conditions developed for conventional solution-phase reactions can be easily adapted for fluorous synthesis.[53]

As a heating source, microwave irradiation has been employed in the development of numerous fluorous chemistry reactions. The microwave synthesis offers advantages of reduced reaction time, improved product yield and selectivity, and minimal amounts of reaction solvent.[54] MCRs generate multiple bonds in a single reaction process, which is a highly efficient way to construct complicated molecules. Performing post-condensation modifications further increases the molecular complexity and molecular diversity.[55]

A fluorous MCR-initiated synthesis of 3-aminoimidazo [1,2-$\alpha$]pyridine/pyrazine **24** is highlighted below. First fluorous benzaldehydes **21** were mixed with 2-aminopyrimidines **22** and cyclohexyisonitrile **23** in a MCR reaction (Scheme 12) facilitated by microwave irradiation.[56] Product were purified by F-SPE. Two kind of cross-coupling reactions were performed, Suzuki cross-coupling with boronic acids to form biaryl compounds **27** and coupling with thiols to form aryl sulfides **28**.

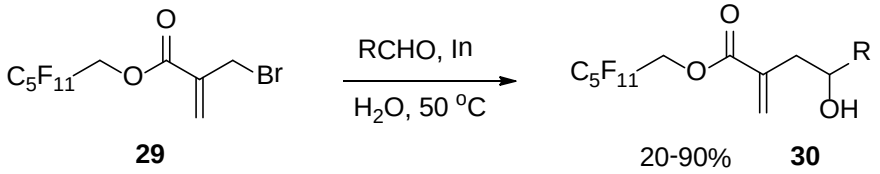



$R^1$ = {H, *p*-$OSO_2C_8F_{17}$}, {H, *m*-$OSO_2C_8F_{17}$}, {*m*-MeO, *p*-$OSO_2C_8F_{17}$}, {*p*-MeO, *m*-$OSO_2C_8F_{17}$}
$R^2$ = {H, X=CH}, {H, X=N}, {*3*-Me, X=C}, {*2*-Me, X=CH}, {*2*-Cl, X=CH}
$R^3$ = Cy, $C_4H_9$, $CH_2Ph$
$R^4$ = *p*-Cl, *m*-CHO.
$R^5$ = *p*-OMe, Cy.

Scheme 12. Microwave-assisted synthesis of 3-imidazopyridine derivatives by MCR and post condensation reactions

Fluorous chemistry has the potential to use water as the primary solvent for both reactions and separations. Because water is inexpensive and nontoxic, using it as a solvent for small-scale synthesis has its own advantages of low cost, nonflammable, and the nontoxic nature of water.[57]

The combination of aqueous reactions and F-SPE purification has been demonstrated in indium-mediated allylation of aldehydes with fluorous bromides **29** (Scheme 13).[58] The reaction mixture containing compound **30** was directly loaded onto fluorous silica gel and isolated by a gradient elution using water and ethanol .




**29** 20-90% **30**

Scheme 13**.** Water-based reaction for allylation of aldehydes

Fluorous chemistry is poised to advance from a niche research area to a broad based suite of tools to solve important synthesis and separation problems. Increasing availability of varieties of fluorous compounds and separation media will make fluorous techniques more accessible. Additional R&D in academic and industrial settings is needed to realize the potential fluorous chemistry in large scale settings.

## 2.4. Microwave-assisted synthesis

Microwave-assisted organic synthesis (MAOS) is a powerful method for chemists that can achieve results faster than the traditional conductive heating methods. Reactions times in the best cases have been reduced from days or hours, to minutes.[60] There have been many new results, of chemical reactions using MAOS, which is demonstrated by exponential growth of the published papers in the scientific literature.[61]

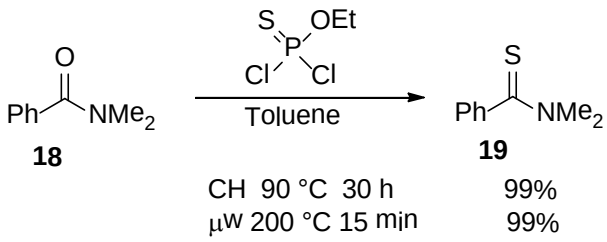
In the pharmaceutical industry the most important feature is the development of procedures which increase efficiency of drug discovery and research. From the standpoint of synthetic chemistry, the use of microwaves as an energy source has shown the following advantages.[60]

- Amplified reaction rates.
- Accelerated chemistries in multi-phase reactions.
- Enhanced product yields.
- Wide quantity scale (few milligrams to multi gram quantities).
- Access to synthetic transformations not achieve via conductive heating.
- Extensive temperature range.
- Green chemistry applications: supercritical water or solvent free reactions.
- Rapid controlled method of heating.
- Direct reaction optimization.

The field of MAOS has been driven by the interests of the chemists looking to expand its boundaries. The use of microwaves as an energy source or pharmaceutical industry applications already is starting to shape the areas of proteomics and pharmacokinetics.[62]

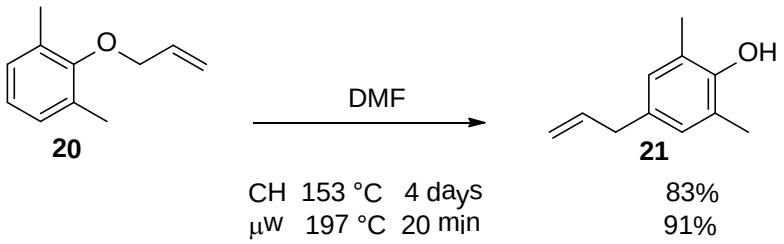
Traditional or conductive heating relies on a thermal energy source directly applied to the reaction vessel. Conductive Heating (CH) is inefficient and slow but is widely applicable. Basically, conductive heating it is a straightforward method.[63] Some of the drawbacks of this method are the inefficiencies of ramping-up temperature, lack of fine control over the reaction heat and the time needed for the cooling.[61] Alternatively microwave heating is fast and can be remotely controlled. Reaction solutions are heated via the direct coupling of microwave energy with either the solvent or reagents in solution and turning this energy into heat. The microwave energy is much less than the typical bond-dissociation energies of organic moieties.[60]

In this study, few examples of advantages of microwave compared with conventional heating are presented. Ley and co-workers[64] described the preparation of thioamides **19** from amides **18**. Although the reaction under classical conditions occurs in excellent yield, the reaction time can be shortened using microwave irradiation (Scheme 14).



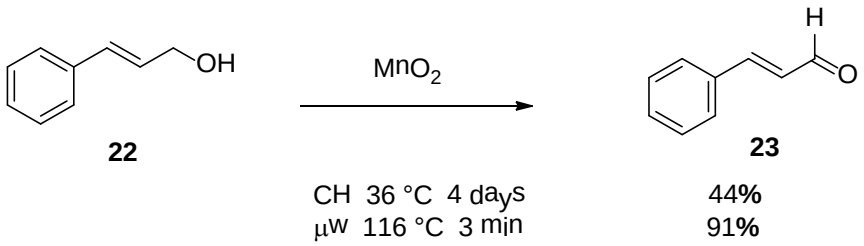

Scheme 14**.** Preparation of thioamides

Next example represent a *para* -claisen rearrangement (Scheme 15) where the microwave reaction has shorten the time of the reaction from days into minutes with better yield.[65]



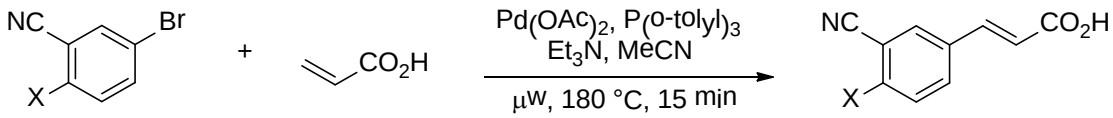

Scheme 15. Tautomerization of allyl phenylether to a *para*-substituted phenol

As last example, the oxidation of tertiary alcohols **22** results in the carbonyl containing compounds **23** (Scheme 16). Here the yields are almost doubled and the reaction times are significantly reduced.[65]




Scheme 16. Oxidation of tertiary alcohols in the carbonyl containing compounds

Reactions promoted via microwave energy are suited for reaction scoping and rapid reaction optimization. The reaction times in general are in the matter of minutes. This method enables a simple and quick scoping of reaction conditions in required reaction parameters of time, temperature, reagents and solvents. MCRs present suitable procedures for the introduction of structural diversity for the heterocyclic compounds which can be prepared in a single step. Combining MCRs with the kinetics of microwave-assisted organic synthesis offers new methods for the fast and efficient synthesis of heterocyclic libraries which can be used for biological evaluation and furthermore for structure–activity relationship (SAR) studies.[66] Two samples of important findings in MAOS reactions are described. Scheme 17 is an example of a Heck reaction[67] involving aryl bromides **30** and acrylic acid **31** to obtain the corresponding cinnamic acids **32**.[68]




**30a**; X=H
**30**b; X=F

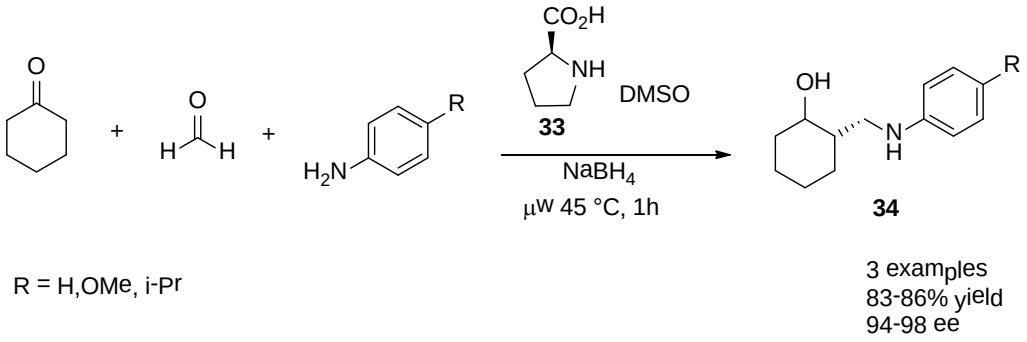
**31**

**32a**; X=H, 82%
**32b**; X=F, 55%

Scheme 17. Microwave-assisted example of Heck reaction

Optimization of the single-mode microwave conditions led to a protocol that used MeCN as the solvent, $Pd(OAc)_2/P(o\text{-tolyl})_3$ as the catalyst system, and triethylamine as the base. The reaction time was 15 minutes at 180 ºC.

The Mannich reaction[12] which is among the most important carbon-carbon bond forming reactions in organic synthesis, suffers from some drawbacks, such as the need for harsh reaction conditions, long reaction times, and sometimes low yields of products.[69] Bolm and Rodríguez in 2006 investigated thermal effects in the (*S*)-proline **33** catalyzed Mannich reaction . By applying microwave heating, reaction times and the amounts of catalyst can be reduced (Scheme 18). The afforded aminoalcohols **34** were obtained in excellent yields and ee´s.[70]

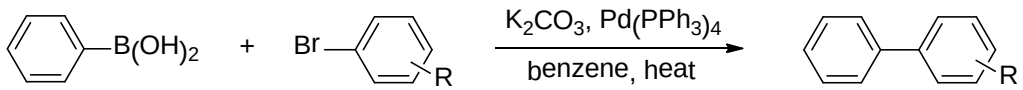



Scheme 18. Microwave-assisted direct asymmetric Mannich reaction

Microwave-assisted organic synthesis is an enabling technology whose potential has not yet been apprehended. It is the obligation of organic chemists to fully implement this method in conjecture with other methods, contemplating the green aspects of the chemical reactions.

## 2.5. Suzuki Coupling

The Suzuki cross-coupling reaction is a useful methodology for generation of carbon-carbon bonds.[71] Usually is a coupling reaction between aryl-boronic acid **25** with an aryl- halide **35** catalyzed by palladium or nickel complexes[72] to afford biaryls **36**. The reaction was first reported by Akira Suzuki and his group in 1979 (Scheme 19).[73]




**35** **36** **37**

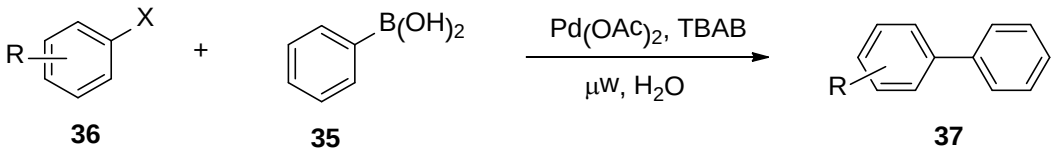
Scheme 19. Suzuki cross coupling between organoboronic acid and halides

Suzuki coupling reaction has immense applications in various fields of chemistry. Formation of synthetic amino acids which are important in the field of biochemistry as building blocks in designing peptide-based biologically active molecules,[74] *anti*-HIV molecules,[75] antibiotics,[76] and solar cell technology.[77] are few examples that show the importance and the diversity of this reaction. Suzuki is one of most familiar palladium-catalyzed reactions mostly because of the nature of boronic acids which generally are non-toxic and stable in room temperature.[78]

Usually an aqueous sodium carbonate is the traditional base used in the reaction but potassium carbonate and cesium carbonate can be used as well.[79] Other features that makes boronates attractive for coupling reaction are easy separation and readily commercially available library which can significantly expand the scope of the reaction.[80]

Suzuki couplings can involve green chemistry aspects, such as reactions which can be performed in aqueous media,[81] use of microwave synthesis,[82] solvent free,[83] ligand free,[84] and the combination of the factors that we mentioned above. The examples which are mentioned represent a part of the scope of Suzuki coupling.

In 2002 Leadbeater and Marco described very rapid, ligand-free, palladium-catalyzed aqueous Suzuki couplings of aryl halides **36** with aryl boronic acids **35** (Scheme 20).[85]

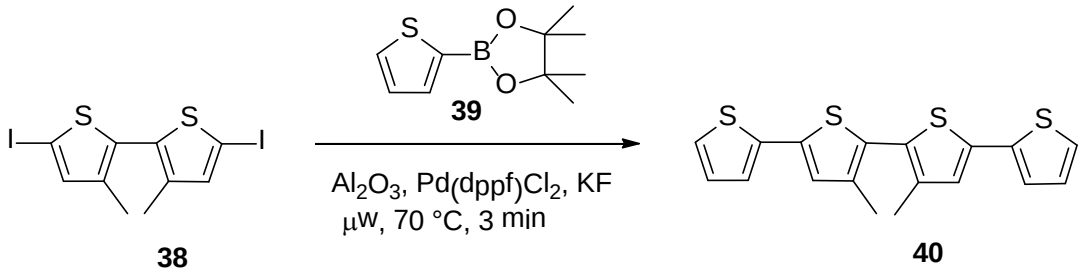



**36** **35** **37**

X = Cl, Br, I
R = H, $CH_3$, $OCH_3$, $NO_2$

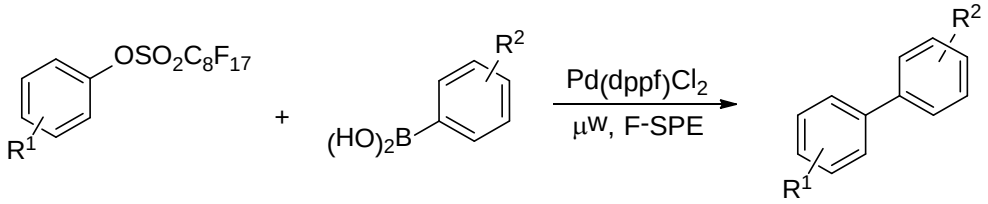
Scheme 20. Ligand-free Suzuki reactions with TBAB as an additive

Barbarella and coworkers have reported a rapid, efficient, and environmentally friendly methodology for the synthesis of pure thiophene oligomers **40** with excellent yields (Scheme 21).[86] The reaction occurs for a very short time by employing a solvent-free, microwave-assisted coupling of thienyl boronic acids **39** with thienyl iodides **38**.



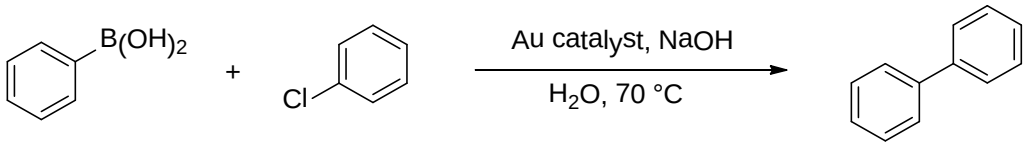

Scheme 21. Solvent-free, microwave-assisted synthesis of thiophene oligomers

In 2004, Zhang and coworkers[87] developed a Suzuki coupling reaction which displaced a fluorous linker to form a new carbon-carbon bond (Scheme 22) by combining fast microwave reaction with easy fluorous chemistry separation technique. The perfluorooctylsulfonate tagged molecules were subjected to aryl boronic acids with a palladium catalyst to form biaryls. The separation was done by F-SPE.




Scheme 22. Suzuki coupling using fluorous synthesis and microwave

In 2009 Guo and coworkers reported on a Suzuki coupling reaction using as a catalyst gold nanoparticles (Scheme 23).[88] The gold catalyst can be recovered by filtration and reused without significant loss of catalytic activity for long periods of time.

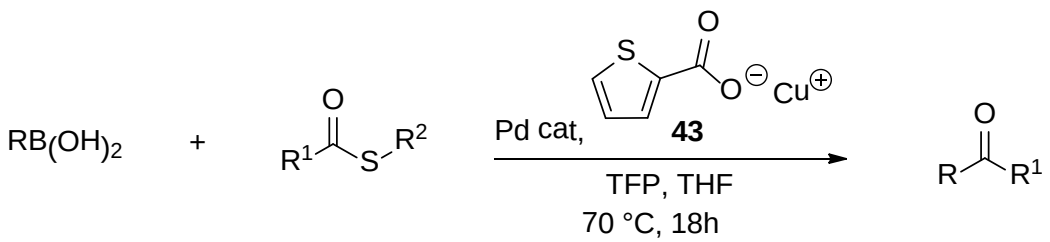



Scheme 23. Suzuki coupling of chlorobenzene and phenylboronic acid using gold nanoparticles as catalyst

## 2.6. Liebeskind-Srogl Coupling

Heterocyclic structures have played an important role in the pharmaceutical industry as well as academic research.[89] Metal-catalyzed coupling reactions are turned into powerful tools for chemists and have proved highly successful in the composition of heteroaromatic sequences.[90]

However, the ability to form site specific bonds within a molecule under mild conditions, without the need for protection or deprotection groups remains a challenge for organic chemists.[91] In general, transition metals coupling procedures involve the interaction of an electrophilic organohalide with a nucleophilic organometallic reagent.[92] The limited stability of the corresponding heteroaromatic byproducts appears to some extent problematic.[93] In 2000, Liebeskind and Srogl discovered a new efficient palladium-catalyzed coupling reaction (Scheme 24) involving thiol esters **43** and boronic acids to obtain ketones.[94] For this method a stoichiometric amount of thiophene-2-carboxylate (CuTC) was needed and did not required a base, unlike the traditional Suzuki cross-coupling, where base is required to activate transmetallation.[95,96] This reaction has been extended to a number of substrates such as alkynes,[97] heteroaromatics,[98] heteroaryl amidines,[99] and functionalized pyrimidinones.[100]




Scheme 24. Liebeskind-Srogl coupling reaction

By using MAOS in MCRs in conjunction with other features such as fluorous technologies, saves significant laboratory time, simplifies the reaction requirements, and makes possible for the building blocks to be selectively transformed into different classes of compounds. This fact is relevant for heterocyclic reactions. The use of protic solvents, leads to quicker, greener and more environmentally friendly chemistry.[101] These days the challenge for an organic chemist is not only to perform large scale MCR, for a production of distinct molecular scaffolds but also to outline the reaction conditions to carry specifically targeted compounds. In the future, advancements will be substantial and MCRs will be a useful synthetic method to generate composite products.

# CHAPTER 3

# RESULTS AND DISCUSSION

## 3.1. Introduction.

In the previous chapters some examples of the pyridine and thiopyridine biological activities are described. There is an elevated interest from scientists today on this type of molecule.[102] That is why the development of environmental friendly and economically viable methods to produce them, is important. There are several factors such as low yields, high temperatures, several steps, long times required to finish the reaction and the use of strong oxidative poisonous and corrosive agents.[36] to acquire DHMPs.

Our challenge is that wherever is possible to design benign methods and use safer chemicals achieve higher yields in a single step effectively. In this thesis one will see that our efforts were concentrated in investigation and the design of novel methods to carry out the reactions in a one-pot multicomponent synthesis of condensation, cycloadition, substitution and coupling reactions combining the easy separation of fluorous molecules and microwave technology. Fluorous technologies are of increasing interests because the immense benefits include the ability to purify all fluorous-containing products from non-

fluorous starting materials using identical chromatographic procedures. Also it allows for "single pot" reactions, where multiple substrates can be transformed in a single reaction mixture, then separated from one another via a fluorous column. Application of the factors that we mentioned above provides a significant improvement in energy consumption reduction, achieving high yields selectivities, as result reactions are greener, with excellent purities and easy separation of products. [103,104]

The tools and the methods described in this study can be used in organic chemistry applications and hopefully will provide successful methodologies for preparation of a variety of DHPM derivatives.

## 3.2. Synthesis of Perflorooctyl Sulfonate benzaldehydes.

### 3.2.1 Introduction

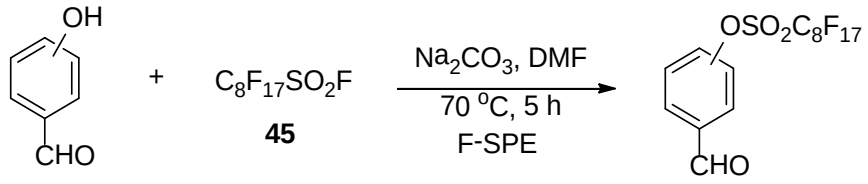
One of the conditions used in the ideal synthesis is the use of readily available compounds.[105] From the three-component of Biginelli reaction urea and $\beta$-ketoester derivatives are available to use and is the perfluorooctanesulfonyl benzaldehyde.

Perfluorooctanesulfonyl benzaldehydes present the fluorous linker to facilitate F-SPE.[106] Intermediates with a fluorous link can be quickly isolated from the reaction mixture. These aryl perfluoroalkylsulfonates can serve as protecting groups to hide active functional groups in unstable reaction conditions.[107] They are also good substrates for metal-catalyzed coupling reactions such as Suzuki coupling, Buchwald-Hartwig[108] amination and coupling with thiols.[109]

### 3.2.2. Results and discussion

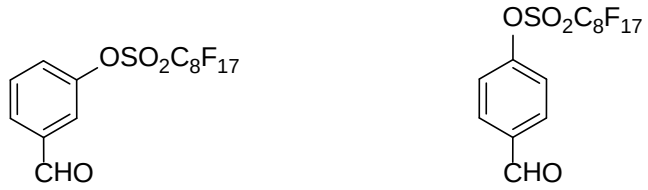
To produce fluorous linked benzaldehydes a well established protocol[88] was used. Benzaldehydes were mixed with perfluorooctanesulfonyl fluoride **45** and $Na_2CO_3$ in dimethylformamide (DMF) and the mixture was heated at 70 $^oC$ for 5-8 hrs. The yields were checked continuously by TLC and LC-MS. The reaction mixture was then extracted by using 1:1 ethyl acetate AcOEt/$H_2O$. The perfluorooctanesulfonyl benzaldehydes **46** and **47** (Fig. 4) were purified by F-SPE (Table 1). The yields were checked continuously by TLC and LC-MS. Products **46** and **47** after purification were used in MCR to synthesize DHPM derivatives.

Table 1. Synthesis of perfluorooctanesulfonyl benzaldehydes[a]




| Entry | -OH | Time (hrs) | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | *m*-OH | 5 | **46** | 89 |
| 2 | *p*-OH | 8 | **47** | 91 |

[a]Reagents and conditions: hydroxybenzaldehyde (6.0 mmole), $Na_2CO_3$ (6.3 mmole), (5.0 mmole), DMF (5.0 mL), [b]Isolated yield after F-SPE.




**46** **47**

Figure 5. Perfluorooctanesulfonyl benzaldehyde products

## 3.3. Synthesis of dihydropyrimidin-2-(1*H*)-one derivatives

### 3.3.1 Introduction

The classical approach to the synthesis of dihydropirimidines through Biginelli reaction, the work to improve the yields and extend the scope has been reported time to time. These methods had something in common like low and variable yields and limited substrate scope. Armed with a better the mechanistic explanation of the reaction by Kappe in 1997 significant advancements were made toward getting better yields.[35] Stadler and Kappe by using automated chemistry were able to make 48 compounds with excellent yields in 12 hours using Lewis acids as catalysts.[110] Also Dallinger and Kappe reported in *Nature* optimized conditions for generation of a small library of 12 DHPM derivatives via one-pot three-component Biginelli cyclocondensation.[111] With microwave heating under sealed vessel conditions, the synthesis of DHPMs were delivered in short reaction times, 10–20 min. per reaction using $Yb(OTf)_3$ as catalyst and as solvent acetonitrile, achieving high yields. Based on literature that we cited above a convenient one-pot synthesis of dihydropyrimidines using different starting materials like benzaldehydes, methyl acetoacetate, and methylurea, was reported (Fig. 5) using $Yb(OTf)_3$ as catalysts and acetonitrile as solvent. The approach used, results in high yields minding few green aspects like the effectiveness of MCRs and the efficiency of microwave irradiation. All of this is combined with quick and effective way of isolation of main products that fluorous chemistry offers through F-SPE. The products obtained are functionalized dihydropyrimidine and thiopyrimidine derivatives which later are exposed to modifications like cycloadditions, Suzuki and Liebeskind-Srogl coupling.

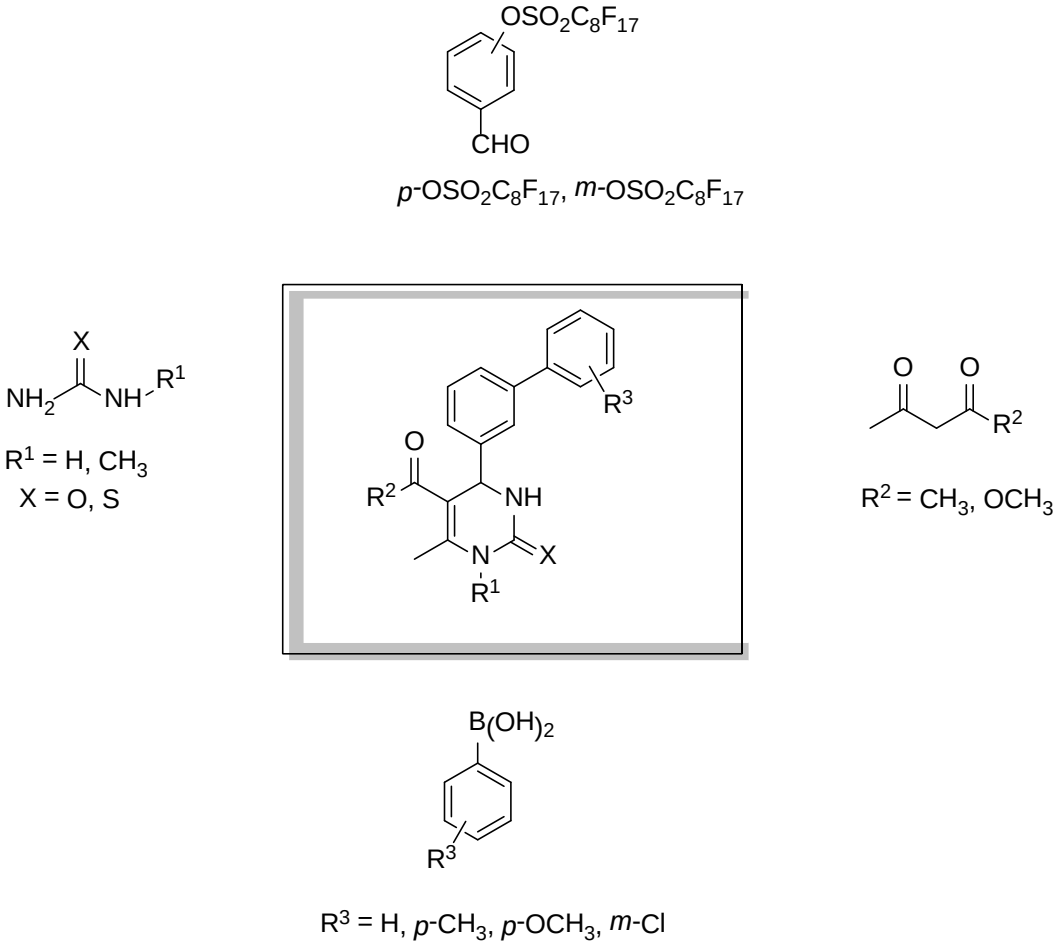



Figure 6. Building blocks for preparation of substituted DHPM derivatives

### 3.3.2 Results and discussion

Because of importance scaffolds of dihydropyrimidinones there is an abundance of literature examples which gave a head start for our reaction. The intricacy of fluorous tag present in the molecule requires finding of optimal conditions for at least one of the reactions and by exploring the change of one element in this reaction. We tried to extend the number of products that we were getting for the same reactions. The results from

were checked by TLC and Agilent LC-MS 1200 series. Initial studies were focused on the one-pot three-component condensation of *m*-$OSO_2C_8F_{17}$, **46** acetylacetone, and methylurea using $Yb(OTf)_3$ as catalyst in acetonitrile (Scheme 25).

In order to find the optimal conditions for the reaction parameters were carried out several experiments using fluorous benzaldehyde as a limiting agent. The temperature, solvent ratio was chosen based on condition experiments made by Kappe and coworkers[111] and the effects of reactant ratios were studied. During the test experiments was found that methylurea was slightly more active than ketoesthers because it produced more intermediates when used with the same ratios (Table 2).

Table 2. Effect of equivalence of starting materials on the microwave-assisted MCR to synthesize tetrahydroyrimidines

| F-Sulfonyl (eq.) | Methylurea (eq.) | Acetylacetone (eq.) | Yield (%)[a] |
|---|---|---|---|
| 1.0 | 1.5 | 1.5 | 64 |
| 1.0 | 1.5 | 1.2 | 58 |
| 1.0 | 1.2 | 1.5 | 85 |

[a]Estimated yield established by LC-MS

For the best condition, methylurea **48** was not more than 1.2 equivalence excess of limiting agent and ketoesther **49** in the excess amount of 1.5 equivalents.

One-pot reactions with microwave between various aldehydes, ketoesthers, methylurea were tried and the results were recorded. The reactions were promoted by $Yb(OTf)_3$ as a catalyst acetonitrile as a solvent, and under microwave irradiation at 120º C for 20 min. The optimized condition was developed after exploring other solvents including water, EtOH and toluene, and different microwave reaction temperatures (100-130 $^{o}$C) and times (10-20 min) (Table 3).

Table 3. Effect of reaction time and temperature on the microwave-assisted synthesis of fluorous dihydropyrimidine derivatives

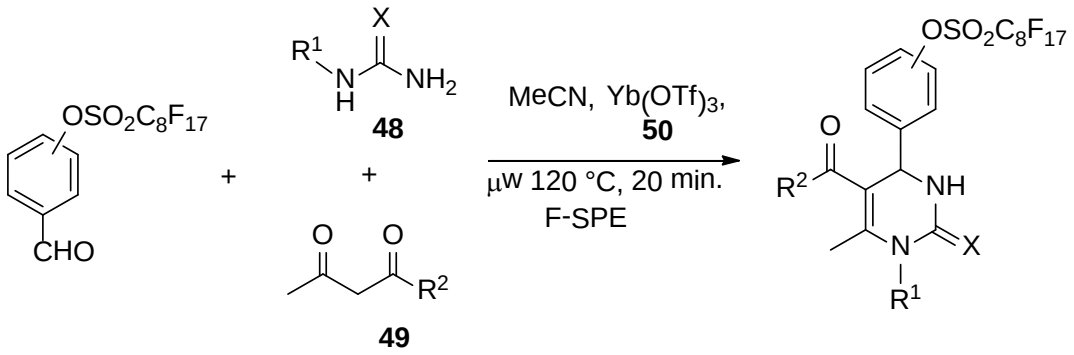
| Solvent | Time (min) | Temp ($^{o}$C) | Yield (%)[a] |
|---|---|---|---|
| Water | 10 | 100 | 0 |
| Ethanol | 10 | 100 | 5 |
| Ethanol | 15 | 120 | 8 |
| Ethanol | 20 | 130 | 13 |
| Toluene | 10 | 100 | 18 |
| Toluene | 15 | 100 | 25 |
| Toluene | 20 | 120 | 33 |
| Toluene | 20 | 130 | 45 |
| Acetonitrile | 10 | 100 | 52 |
| Acetonitrile | 15 | 100 | 52 |
| Acetonitrile | 15 | 120 | 58 |
| Acetonitrile | 20 | 120 | 75 |
| Acetonitrile | 20 | 130 | 68 |

[a]Estimated yield established by LC-MS

Final products were purified using F-SPE. During the experiments was observed that the position of the fluorous tag in the ring of benzaldehyde is important. While not significant differences for the F-sulfonyl in the *para* and *meta* positions the reaction with

the fluorous tag in the *ortho* position did not give a reaction (Table 4, Entry 5). This could be explained with the fact that perfluorooctosulphonyl is a large molecule and being in the *ortho* position will interfere with the steric hindrance of the DHPMs that is formed during the reaction.

Table 4. Biginelli reactions of fluorous dihydropyrimidinones and dihydropyrimidinethiones




| Entry | F-Sylfonyl | $R^1$ | $R^2$ | X | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | *m*-$OSO_2C_8F_{17}$ | $CH_3$ | $CH_3$ | O | **51** | 91 |
| 2 | *m*-$OSO_2C_8F_{17}$ | $CH_3$ | $OCH_3$ | O | **52** | 95 |
| 3 | *p*-$OSO_2C_8F_{17}$ | $CH_3$ | $CH_3$ | O | **53** | 90 |
| 4 | *p*-$OSO_2C_8F_{17}$ | $CH_3$ | $OCH_3$ | O | **54** | 88 |
| 5 | *o*- $OSO_2C_8F_{17}$ | $CH_3$ | $CH_3$ | O | **55** | 0 |
| 6 | *m*-$OSO_2C_8F_{17}$ | H | $CH_3$ | S | **56** | 89 |
| 7 | *m*-$OSO_2C_8F_{17}$ | H | $OCH_3$ | S | **57** | 85 |

[a]Isolated yield after F-SPE.

By substituting the methylurea with urea the protocol was extended to afford formation of thiopyrimidine derivatives (Table 4, Entry 6, 7). Two analogues **56** and **57** were obtained with slightly lower yields than the dihydropyrimidinones derivatives **51-54.**

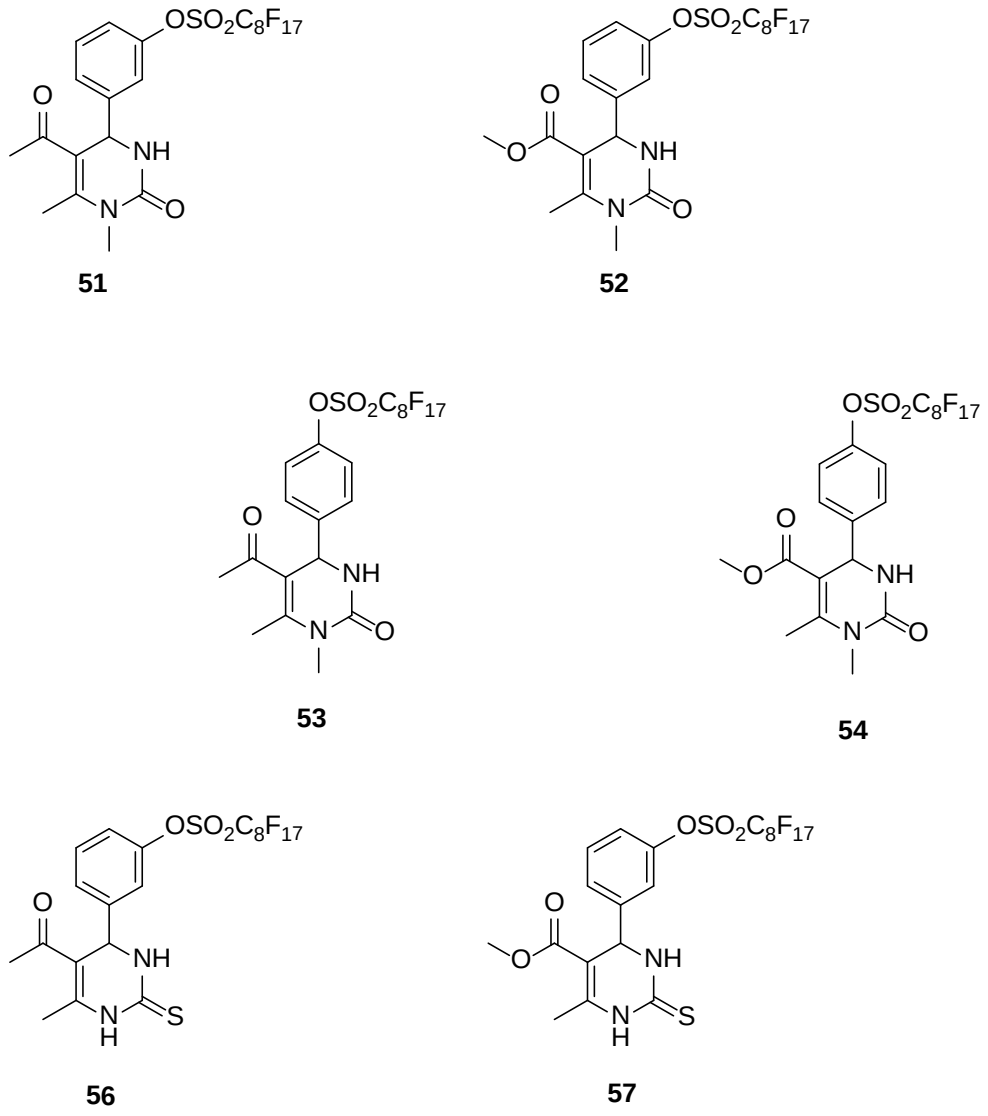



Figure 7. Fluorous dihydropyrimidinones and dihydropyrimidinethiones.

In summary six Biginelli products were prepared (Table 4) in 85-95% yields. The reaction mixtures were purified by F-SPE. The non-fluorous reagents were washed out by 80:20 MeOH-$H_2O$ and fluorous DHPMs were collected by eluting with 100% MeOH/acetone.

The described above one pot Biginelli condensation reaction approach represents an efficient protocol for synthesis a variety of DMHPs from different building blocks. This method provides high yields and good selectivities in short times. The use of microwave, for short and energy efficient reactions, fluorous tags for fast and trouble-free product isolation features some green chemistry elements to the synthesis of target compounds. [112] As a next step Suzuki coupling with biaryls to increase the diversity the DHPM scaffold was tried.

## 3.4. Suzuki reaction of DHPMs

### 3.4.1 Introduction:

Aryl halides are one of the most common substrates used in palladium catalyzed coupling reactions.[113] In our experiments the fluorous tag was employed instead of the halides. Beside the fact that perfluorooctanesulfonyl group offers a simplified purification, has multifunctional role during the Suzuki coupling. At the first stage of reaction it protects the hydroxyl group of boronic acids and later serves as an activation group for phenols during cross coupling and furthermore offers high solubility in common organic solvents and their thermostability makes fluorous molecules good candidates for solution-phase microwave reactions.[88]

[$Pd(dppf)Cl_2$] (dppf = 1,1'-bis(dipenylphospanyl)ferrocene)was employed as a catalyst. $Pd(dppf)Cl_2$ is a very useful catalyst for the cross-coupling reactions of vinyl or aryl halides or triflates with Grignard reagents, leading to carbon–carbon bond formation.[114] Overall this catalyst is air and moister stable have longer shelf life and is easier to handle that other Pd catalysts.[115]

### 3.4.2 Results and discussion

In our initial experiment fluorous dihydropyrimidinone **50**, was used as limiting reagent. 4-methoxyboronic acid (1.5 eq), **25** cesium carbonate ($CsCO_3$) **58**(2.5 eq.), and 1mol % catalytic amount of $Pd(dppf)Cl_2$ **59** and 4:4:1acetone:toluene:water as co-solvent

was added. The mixture was heated under microwave irradiation in temperature 130 ºC for 10min.[88]

To further optimize the initial protocol, experiments with different times and temperatures were tried (Table 5). Reactions were monitored by LC-MS. The best result was achieved when microwave heating reached 140 $^{o}$C for 30 min.

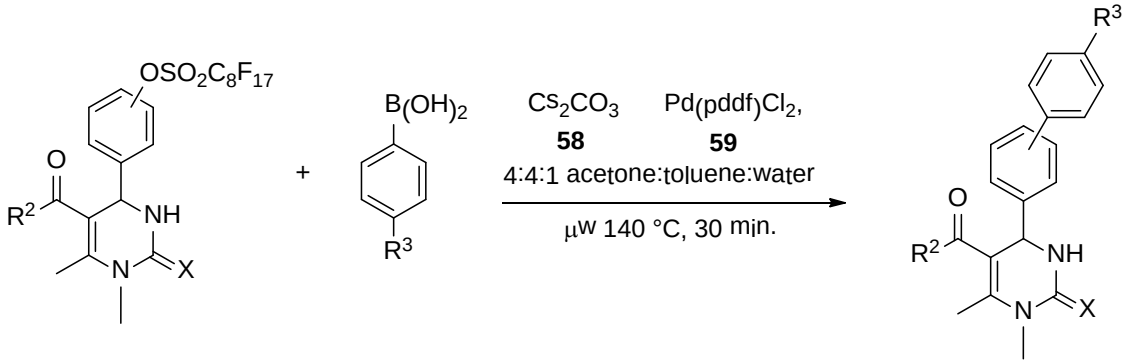
Table 5. Effect of time and temperature on microwave-assisted Suzuki coupling reaction.

| Time (min) | Temp ($^{o}$C) | Yield (%)[a] |
|---|---|---|
| 10 | 130 | 0 |
| 20 | 130 | 10 |
| 25 | 130 | 15 |
| 30 | 130 | 23 |
| 30 | 140 | 42 |
| 20 | 160 | 34 |

[a]Estimated yield established by LC-MS

The reaction best performed at 140 ºC for 30 min, at the end there were no traces of the starting material left and the removal of the fluorous tag was complete .In order to investigate the scope of the reaction, available fluorous dihydropyrimidinones and dihydropyrimidinethiones were subjected to Suzuki coupling with arylboronic acids under optimized conditions. For each fluorous DHMP we used two aryl boronic acids. Reaction between dihydropyrimidinethiones and aryl boronic acids was not observed (Table 5, Entry 9, 10).

Table 6. Suzuki-Miyaura cross-coupling reaction of biaryl-substituted dihydropyrimidinones[a]




| Entry | X | $R^2$ | $C_8F_{17}O_2SO$- | $R^3$ | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | O | Me | *m*-$OSO_2C_8F_{17}$ | OMe | **60** | 67 |
| 2 | O | Me | *m*-$OSO_2C_8F_{17}$ | H | **61** | 56 |
| 3 | O | OMe | *m*-$OSO_2C_8F_{17}$ | OMe | **62** | 57 |
| 4 | O | OMe | *m*-$OSO_2C_8F_{17}$ | H | **63** | 51 |
| 5 | O | Me | *p*-$OSO_2C_8F_{17}$ | OMe | **64** | 68 |
| 6 | O | Me | *p*-$OSO_2C_8F_{17}$ | H | **65** | 62 |
| 7 | O | OMe | *p*-$OSO_2C_8F_{17}$ | OMe | **66** | 58 |
| 8 | O | OMe | *p*-$OSO_2C_8F_{17}$ | H | **67** | 60 |
| 9 | S | Me | *m*-$OSO_2C_8F_{17}$ | H | **68** | 0 |
| 10 | S | OMe | *m*-$OSO_2C_8F_{17}$ | H | **69** | 0 |

[a]Reagents and conditions: fluorous dihydropyrimidines (0.1 mmole), phenyl boronic acid (0.15 mmole), Cesium carbonate (0.25 mmole), Pd catalyst (0.01 mmole), co-solvent (3 mL),[b]Isolated yield after flash chromatography.

There was no difference in yields observed between the *para* and *meta* position of fluorous tag in the molecule.

In conclusion a general method for Suzuki coupling of perfluorooctanesulfonyl dihydropyrimidinones with phenyl boronic acids was developed using commercially available components, $Pd(dppf)Cl_2$ as catalysts and $Cs_2CO_3$ as base. Four dihydropyrimidinones **51-54** gave eight Suzuki products **60-67** in 51-68% yield after F-SPE and flash chromatography purification. However, no reactions ensued to the dihydropyrimidinethiones **56,57** under the same reaction condition. Alkyl-boronic acids used in Suzuki coupling reaction are one of a few compound classes that are air-stable materials of relatively low toxicity that undergo C-C bond formation in the presence of a wide variety of functional groups.

The Suzuki reaction of 3,4-dihydropyrimidinethiones was not observed. One reason is that the thiocarbonyls which are very reactive species[116] first reacts with the Pd catalyst and poisoning it. Thus the Suzuki coupling cannot happen. One way to address this problem, is to lessen the reactivity of C = S bond by performing an oxidation reaction on dihydropyrimidine-thiones.[117]

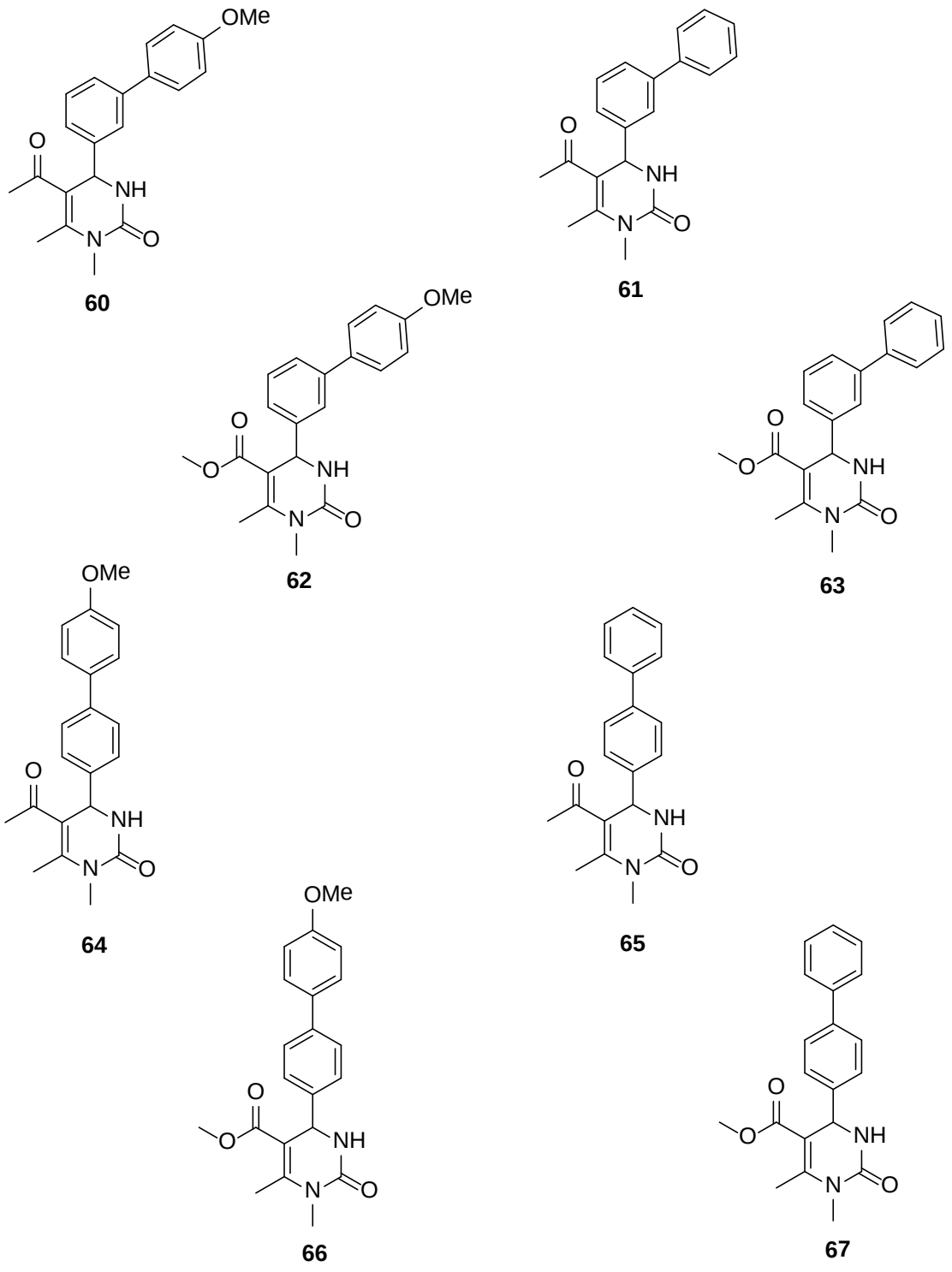


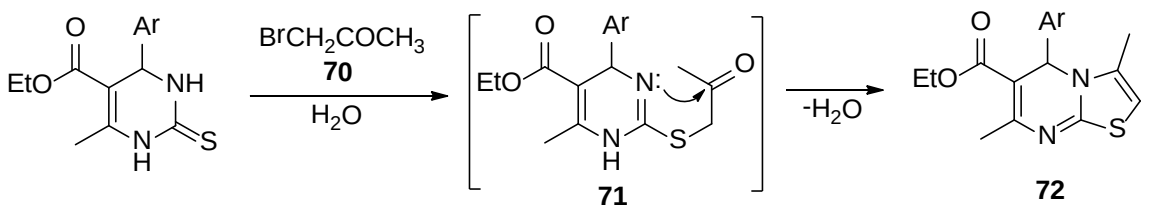

Figure 8. Biaryl-substituted dihydropyrimidinones obtained from the Suzuki-cross coupling reaction

## 3.5. Synthesis of 5H-Thiazolopyrimidines.

### 3.5.1 Introduction

A cycloadition reaction to a Biginelli structure of dihydropyrimidine- thiones would serve two purposes. The first one is to increase the scope of the manipulation of the dihydropyrimidine scaffold, obtaining compounds which have interests as synthetic and natural products for their channel blocking activity.[118] The second purpose is to overcome the deleterious effects of the double bonded sulfur on the structure of dihydropyrimidine- thiones. Actually the scope of this reaction is not fully investigated and first methodologies involve long reaction times and low yields.[119]

Xi-Cun Wang and coworkers reported an efficient method to obtain thiazolopyrimidines from cyclization reaction (Scheme 25) of dihydropyrimidinethiones with α-bromoacetone in aqueous media under reflux condition for 4 hours.[120, 121] The driving force behind this reaction is the nucleophilic addition of sulfur of dihydropyrimidinethione to the α-bromoacetone giving species **71**. The formed interimediate **71** undergoes through addition-elimination to give dihydropyrimidinethiazole **72**. HCl acts as a catalyst for the condensation step after the ring closure. According to Kappe the regioselectivity of the addition-cyclization step, happens because of a difference in the electron density of nitrogens in the position 1 and 3 of 3,4-dihydropyrimidine-thione [122] The high electron density of the $N^3$ atom results in exclusive addition-cyclization at this position.




Scheme 25. Synthesis of 5*H*-thiazolo[3,2-*α*]pyrimidines in water.

Organic synthesis in aqueous media is gaining importance because of the fact that the use of many toxic and volatile organic solvents, contributes to pollution. From a green chemistry point of view it is highly desirable to develop environmentally benign processes that can be conducted in aqueous solution. Furthermore, using water as a solvent offers many advantages, such as simple operation and high efficiency in many organic reactions that involve water-soluble substrates, reagents, and renewable materials. Recently, many reactions that were believed to occur only in organic solvent have been developed to run in water.[123, 124]

In our trials we tried to extend the green aspect of this reaction by exploiting the benefits of microwave irradiation to increase selectivities and shorten the reaction time. In these experiments was used chloroacetone **73** instead of α-bromoacetone **70**.

Herein a new method to prepare thiazolopyrimidines trough cycloadittion reaction of dihydropyrimidine thiones with chloroacetone in aqueous medium using microwave irradiation was reported.

### 3.5.2 Results and discussion

The best candidates to run this reaction are dihydropyrimidinethiones **56**, **57** obtained from Biginelli reaction (Table 4). Because there are no examples of this kind of reaction in microwave an optimum condition regarding time and temperature is needed at the beginning. According to the reference protocol[121] condition was 4hrs in reflux temperature.

The optimization was started with 100 ºC for 10 min. Results were monitored by LC-MS. The best conditions were found when reaction ran at 130 ºC for 25 min (Table 7).

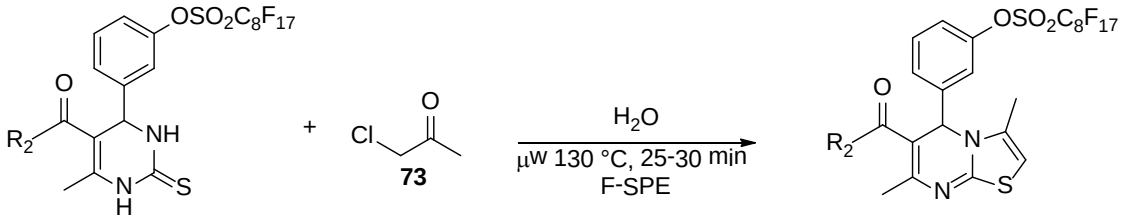
Table 7. Effect of reaction time and temperature on the microwave-assisted synthesis of fluorous dihydropyrimidinethiones

| Time (min) | Temp ($^{o}$C) | Yield (%)[a] |
|---|---|---|
| 10 | 100 | 0 |
| 15 | 100 | 8 |
| 20 | 100 | 15 |
| 20 | 110 | 22 |
| 20 | 120 | 35 |
| 25 | 120 | 47 |
| 25 | 130 | 58 |

[a]Isolated yield after F-SPE.

We stopped optimization at the point that no starting material was left. The reaction mixture quality was checked with LC-MS and was purified by F-SPE. The results are expressed in the Table 8.

Table 8. Microwave-assisted synthesis of thiazolopyrimidines in water.

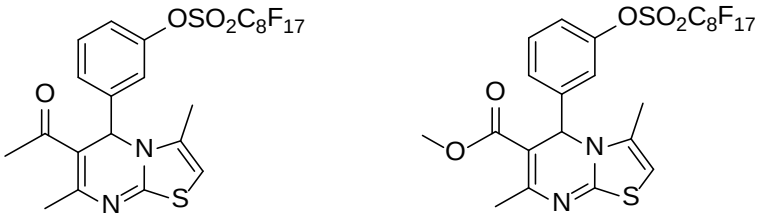



| Entry | $R^2$ | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | Me | **74** | 89 |
| 2 | OMe | **75** | 85 |

[a]Isolated yield after F-SPE.

In summary 5*H*-thiazolo[3,2]pyrimidines can be efficiently prepared by reaction of dihydropyrimidinethiones with chloroacetone in water media. Two analogues were prepared in very good yields The easiness and the efficacy of this method provides an attractive route to the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives. An additional time of 5 min needed for the scale-up reaction.

After a careful search in the literature no other method was found to prepare 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives through the reaction of dihydropyrimidinethione with chloroacetone, using water as the solvent under microwave irradiation.



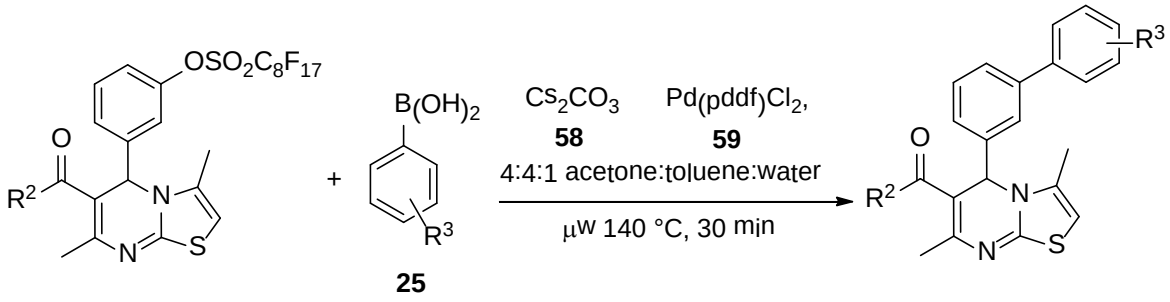

**74** **75**

Figure 9. Thiazolopyrimidine products of cycloaddition reaction in water.

## 3.6. Suzuki reaction of thiazolopyrimidines.

After the successful creation of thiazolopyrimidines **74, 75** the next logic step was to try the Suzuki cross-coupling reactions to remove the floors linker and introduce biaryl groups. Microwave irradiation reactions using the same optimized condition (Table 6) as in the subchapter (3.4.2) using as the limiting reagent thiazolopyrimidines with an excess amount of phenyl boronic acid (1.5 eq.), cesium carbonate ($CsCO_3$) **58** (2.5 eq.), and a catalytic amount of $Pd(dppf)Cl_2$ **59** were performed in the co-solvent 4:4:1 acetone: toluene: water at 140 $^oC$ for 30 min. Each thiazolopyrimidine was exposed to Suzuki cross-coupling with four different boronic acids and eight final analogues were prepared within 55-64% yields. Reaction mixtures were separated by F-SPE and flash chromatography and the results are expresses in the Table 9.

Table 9. Microwave-assisted Suzuki cross-coupling reaction of biaryls with thiazlopyrimidines.

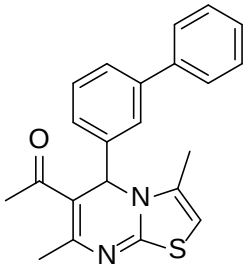



$R^2$ = $CH_3$, $OCH_3$
$R^3$ = H, *p*-$CH_3$, *p*-$OCH_3$, *m*-Cl

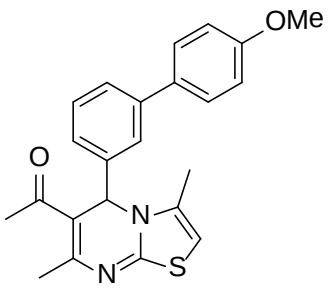
| Entry | $R^2$ | $R^3$ | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1 | Me | H | **76** | 61 |
| 2 | Me | *p*-OMe | **77** | 64 |
| 3 | Me | *m*-Cl | **78** | 56 |
| 4 | Me | *p*-Me | **79** | 62 |
| 5 | OMe | H | **80** | 58 |
| 6 | OMe | *p*-OMe | **81** | 55 |
| 7 | OMe | *m*-Cl | **82** | 63 |
| 8 | OMe | *p*-Me | **83** | 55 |

[a]Isolated yield after flash chromatography

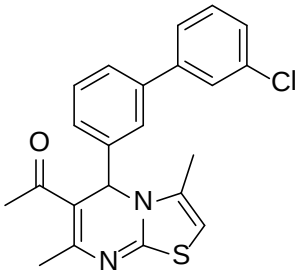
In conclusion a general method for Suzuki cross-coupling of thiazolopyrimidines with phenyl boronic acids was developed using commercially available components, $Pd(dppf)Cl_2$ as catalysts and $Cs_2CO_3$ as base. Two thiazolopyrimidines **74, 75** gave eight Suzuki products **76-83** in good yields (51-68%) after F-SPE and flash chromatography purification. By extending the usage of protocol optimized in the case of dihydropyrimidines to thiazolopyrimidines we save time and reagents, leading toward a general protocol of Suzuki cross-coupling of DHPMs.



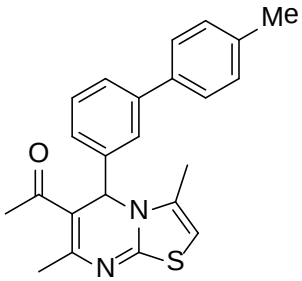

**76**



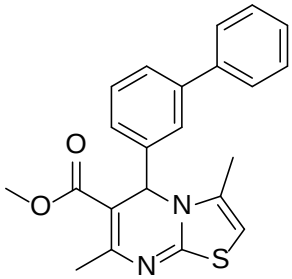

**77**



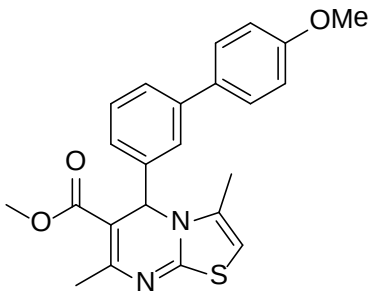

**78**




**79**




**80**

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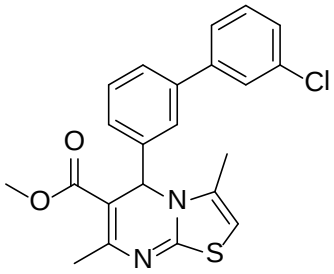
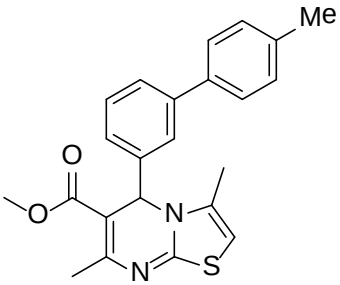



**82**



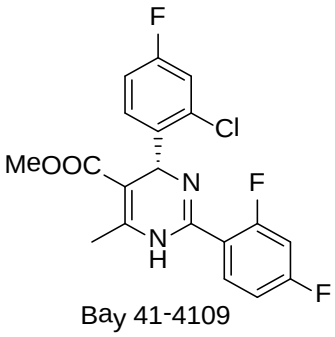

**83**

Figure 10. Biaryl-substituted thiazolopyrimidines

## 3.7. Liebeskind-Srogl coupling.

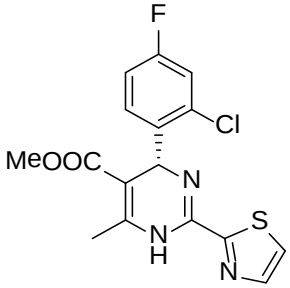
### 3.7.1 Introduction

Multifunctionalized pyrimidines have a wide range of biological activities. Their special structures have also emerged as a building block in natural or synthetic molecules. Some important pyrimidine derivatives (Figure 10) are being used today in clinical trials as hepatitis B virus non-nucleosidic inhibitor, [125] **84**, **85** and **86**, and the potent anticancer drug, **87** a tyrosine kinase inhibitor.[126]



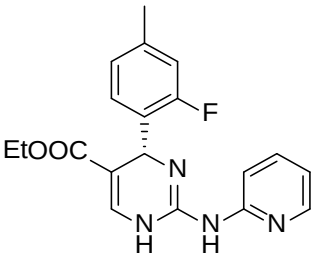

Bay 41-4109

**84**



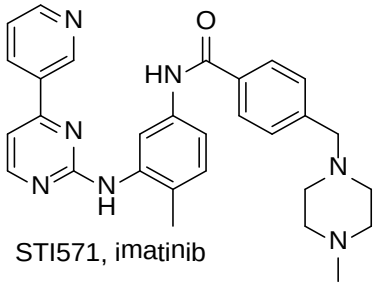

Bay 39-5493

**85**




HAP-1

**86**




STI571, imatinib

**87**

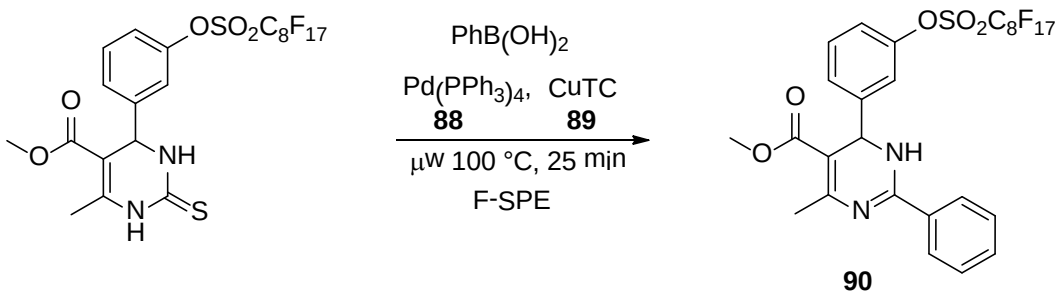
Figure 11. Examples of important dihydropyrimidine scaffolds.

Dihydropyrimidinethiones has been used for the Liebeskind-Srogl coupling reaction with a boronic acid to convert to 2-aryl-1,6-dihydropyrimidine.[97, 127] Kappe and coworkers developed a direct C-C cross-coupling of cyclic thioureas under microwave conditions in high yields.[128]

We explored the Liebeskind-Srogl cross-coupling and we report an efficient palladium catalyzed coupling of dihydropyrimidine-2-thiones with phenylboronic acids. Similar to the cycloaddition reaction (Table 7) described in the subchapter (3.4.2), there are two purposes of employing a desulfative coupling technique. First the scope of the dihydropyrimidine scaffolds in more diverse structures was increased and second by removing the sulfur the palladium-catalyzed Suzuki reaction is facilitated.

### 3.7.2 Results and discussion

Reaction conditions for the Liebeskind-Srogl coupling were defined with respect to method used by Kappe[128] for quick turnout of results. Initially, coupling reactions between boronic acids and dihydropyrimidine-2-thiones were performed under conditions reported by Kappe *et al.* with $Pd(PPh_3)_4$ as catalyst, CuTC as co-catalyst, in THF as solvent, under microwave irradiation in 100 ºC, for 25 min. The reaction worked well using 0.2 mmol of dihydropyrimidine-2-thiones as a limiting agent. This procedure afforded good conversion and good yields of desired product **90**.




**90**

Scheme 26. Liebeskind-Srogl desulfative coupling reaction under microwave irradiation

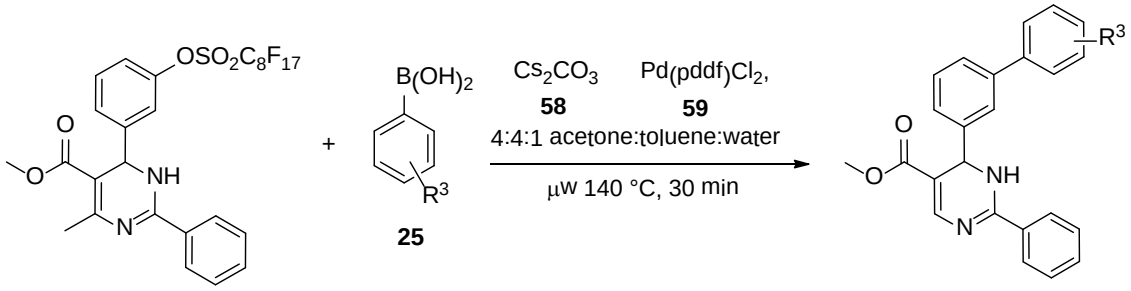
According to the method both reaction time and temperature are important for achieving a good conversion of dihydropyrimidine -2-thione **75** to 2-aryl-1,6-dihydropyrimidine **90**. Although there is more room to optimize the reaction conditions, the fact that the selective arylation of cyclic thiourea at 100 ºC with the used conditions (Scheme 26) affords the desired analogues in reasonable yields was evident.

The described method is a direct C-C coupling of cyclic thioureas with boronic acids under non basic Liebeskind–Srogl reaction conditions (Scheme 26). The desulfitative coupling of dihydropyrimidine-2-thione fragments is considered to be rather difficult, because competing C-S cross-coupling is usually the preferred pathway of such reactions.[129] The key steps of the method involve the Liebeskind-Srogl coupling of cyclic thioureas with boronic acids. Under controlled microwave irradiation at 100 ºC, reaction was completed within 25 minutes and resulted in sufficient yield. A considerable amount (3 equiv.) of the CuTC co-catalyst was needed for the conversion. Although the reaction condition for the Liebeskind-Srogl couplings needs further optimization, the high overall yield makes this procedure applicable for the generation of other new libraries.

### 3.7.3 Suzuki cross-coupling of 2-aryl-1,6-dihydropyrimidines

Microwave irradiation reactions using the same optimized condition (Table 6) as in the subchapter (3.4.2) using as the limiting reagent 2-aryl-1,6-dihydropyrimidine with an excess amount of phenyl boronic acid (1.5 eq.), cesium carbonate ($CsCO_3$) **58** (2.5 eq.), and a catalytic amount of Pd(dppf)$Cl_2$ **59** were performed in the co-solvent 4:4:1 acetone: toluene: water at 140 $^oC$ for 30 min. The obtained 2-aryl-1,6-dihydropyrimidine was exposed to Suzuki cross-coupling with four different boronic acids. Four final analogues were prepared within 55-64% yields. Reaction mixtures were separated by F-SPE and flash chromatography.

Table 10. Microwave-assisted Suzuki cross-coupling reaction of biaryls with the 2-aryl-1,6-dihydropyrimidine

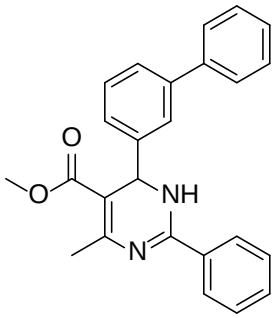



$R^3$ = H, *p*-$CH_3$, *p*-$OCH_3$, *m*-Cl

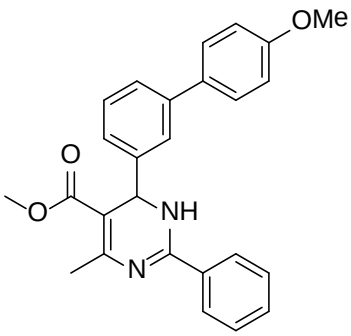
| Entry | $R^3$ | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | H | **91** | 45 |
| 2 | *p*-OMe | **92** | 48 |
| 3 | *m*-Cl | **93** | 31 |
| 4 | *p*-Me | **94** | 48 |

[a]Isolated yield after flash chromatography

A general method for Suzuki cross-coupling of 2-aryl-1,6-dihydropyrimidine with phenyl boronic acids was developed using commercially available components, Pd(dppf)$Cl_2$ as catalysts and $Cs_2CO_3$ as base. 2-aryl-1,6-dihydropyrimidine **90** gave four Suzuki products **91-93** in good yields (31-48%) after F-SPE and flash chromatography purification. The generalized method of Suzuki cross-coupling can be easily adapted to create small libraries.




**90**

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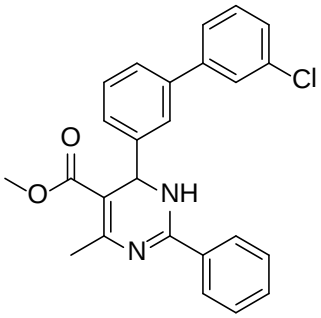


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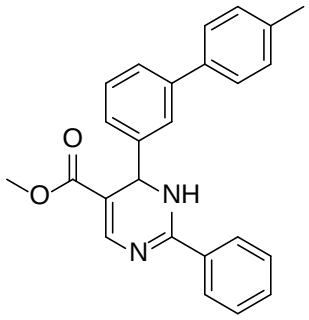



**93**

Figure 12. Biaryl-substituted structures of 2-aryl-1,6-dihydropyrimidine

# CHAPTER 4

# CONCLUSIONS

DHPMS are biologically and therapeutically important class of compounds. In our work, efforts were directed toward creating new methods and useful protocols for synthesis of drug resembling compounds of high interests.

Overall we developed a new application of perfluorooctanesulfonyl-linked benzaldehydes for diversity-oriented synthesis of heterocyclic scaffolds. The intermediates obtained from the Biginelli reaction were used for post-condensation modifications to afford biaryl-substituted dihydropyrimidinone, dihydropyrimidine, and thiazolopyrimidine compounds.

A set of reactions and separation techniques used elements of green chemistry such as multicomponent reactions, microwave heating, and F-SPE and have been employed. The MCRs provide the atom economy aspect and generate multiple bonds in a single reaction process which is an efficient way to construct complicated molecules.

The fluorous sulfonyl linker not only served as a phase tag for quick and efficient F-SPE separation, of fluorous products but also served as a cleavable linker for post-MCR coupling modifications.

Microwave irradiation allowed the reactions to be finished within 30 minutes whereas the traditional way of conventional heating takes days and hours. Microwave heating also improves reaction rates, selectivities and yields. As a result we obtain cleaner products with a minimum of waste production.

In our research we were able promptly to modify available protocols for our experiments and also were able to generalize the method for Suzuki cross-coupling reaction for the three categories of the DHPMs obtained in our research. In return we saved time and materials needed to optimize each method separately.

In the case of dihydropyrimidinethiones we did overcome the obstacle of not being able to perform Suzuki cross-coupling directly. By using modifications such as cycloaddition, and Liebeskind-Srogl desulfative coupling we increased the diversity of the initial scaffold with new elements and were able to go through with the Suzuki reaction. The varieties of products we acquired in good to excellent yields.

The methods described in this work provide by some means, through efficient and environmentally friendly routes the design of small to medium libraries of heterocyclic compounds, which can be used in drug candidate screenings.

The results described in this work are published in following Journals:

1. Piqani, B.; Zhang, W.; “Synthesis of diverse dihydropyrimidine-related scaffolds by fluorous benzaldehyde-based Biginelli reaction and post-condensation modifications” *Beilstein Jour. Org. Chem.* **2011**, *7*, 1294.

2. Kadam, A.; Ding, S.; Piqani, B. Zhang, W. **“**Convertible Fluorous Sulfonate Linker for the Synthesis of Diverse Library Scaffolds**”** *J. Chin. Chem. Soc.* **2011**, *58*, 575.

# CHAPTER 5

# EXPERIMENTAL PROCEDURES

## 5.1. General experimental procedure for synthesis of perfluorooctanesulfonyl benzaldehydes (Chapter 3.2)

All reactants were purchased from Aldrich and used without further purification. The hydroxybenzaldehyde (6 mmol) and $Na_2CO_3$ (6.3 mmol) were dissolved in DMF (5.0 mL) at room temperature. Perfluorooctanesulfonic fluoride (5 mmol) was then added dropwise to the mixture and heated at 70 $^oC$ for 5-8 h. The reaction was monitored by TLC and LC-MS. The finished product was cooled down and extracted with a 1:1 AcOEt:water mixture (100 mL). The combined organic phase was dried over anhydrous $Mg_2SO_4$ and the solvent was evaporated under vacuum. The dry perfluorooctylsulfonyl benzaldehyde was further purified by F-SPE eluted with 120 mL of 80:20 MeOH-$H_2O$ and then 120 mL of acetone.

5.2. General experimental procedure for synthesis of fluorous dihydropyrimidinones and dihydropyrimidinthiones through microwave-assisted reaction. (Chapter 3.3)

A solution of perfluorooctanesulfonyl benzaldehyde (2.0 mmol), methylurea (2.4 mmol), methyl acetoacetate (3.0 mmol) and $Yb(OTf)_3$ (0.2 mmol) in 2 mL of acetonitrile was heated in Biotage Initiator microwave synthesizer at 120 $^oC$ for 20 min. The reaction was monitored by TLC and LC-MS. The resulting mixture was purified by F-SPE eluted with 40 mL of 80:20 MeOH-$H_2O$ and then 40 mL of acetone. The acetone fraction was concentrated to give dihydropyrimidinones.

5.3. General experimental procedure for synthesis of biaryl-substituted dihydropyrimidinones through a typical Suzuki cross-coupling reaction procedure. (Chapter 3.4)

A solution of dihydropyrimidinone (0.1 mmol), 4-methoxyphenylboronic acid (0.15 mmol), $Cs_2CO_3$ (0.25 mmol) and $Pd(dppf)Cl_2$ (0.02 mmol) in 3 mL of 4:1:4 acetone:water:toluene was heated in Biotage Initiator microwave synthesizer at 140 $^oC$ for 30 min. The reaction was monitored by TLC and LC-MS. The resulting mixture was isolated and the product was purified by flash chromatography.

5.4. General experimental procedure for cycloaddition reaction to synthesize 5*H*-thiazolo[3,2-α]pyrimidines (Chapter 3.5)

A solution of 3,4-dihydropyrimidine-thione (1 mmol), chloroacetone (1.5 mmol) in 2 mL water was heated in Biotage Initiator microwave synthesizer at 120 $^{o}$C for 30 min. The reaction was monitored by TLC and LC-MS. The resulting mixture was purified by F-SPE eluted with 30 mL of 80:20 MeOH-$H_2O$ and then 30 mL of acetone. The acetone fraction was concentrated to give dihydropyrimidinethiones.

5.5. General experimental procedure for cycloaddition reaction to synthesize 2-aryl-1,6-dihydropyrimidine. (Chapter 3.7)

A solution of 3,4-dihydropyrimidine-thione (0.20 mmol), phenylboronic acid (0.3 mmol), CuTC (0.6 mmol), and $Pd(PPh_3)_4$ (3 mol %) in 2 mL THF was heated in Biotage Initiator microwave synthesizer at 100 °C for 25 min. The reaction was monitored by TLC and LC-MS. The mixture was purified by F-SPE eluted with 30 mL of 80:20 MeOH-$H_2O$ and then 30 mL of acetone. The acetone fraction was concentrated to give 2-aryl-1,6-dihydropyrimidine.

# APPENDIX A

## GENERAL INFORMATION

The $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at a 300 MHz Varian NMR spectrometer in $CDCl_3$ solvent with tetramethylsilane as the internal standard. The temperature was 25 ºC (accuracy ± 1 ºC) and was controlled by the Varian control unit.

LC-MS spectra were recorded on an Agilent 2100 system. A $C_{18}$ column (5.0 μm, 6.0 × 50 mm) was used for separation. The mobile phases were methanol and water both containing 0.05% formic acid. A linear gradient was used to increase from 25:75 v/v methanol/water to 100% methanol over 7.0 min at a flow rate of 0.7 mL/min. The UV detections were at 210 nm and 254 nm. Mass spectra were recorded in atmospheric pressure chemical ionization.

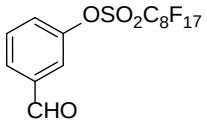
All reactions were carried out in a self-tuning single mode Biotage Initiator microwave synthesizer. Purification of intermediates took place in a Thermo Scientific 16 SPE vacuum manifold.

APPENDIX B

SUPPORTING INFORMATION AND PRODUCT CHARACTERIZATION FOR

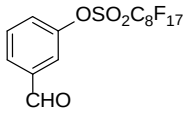
CHAPTER 3.2

**3-Perfluorosulfonyl benzaldehyde (46)**

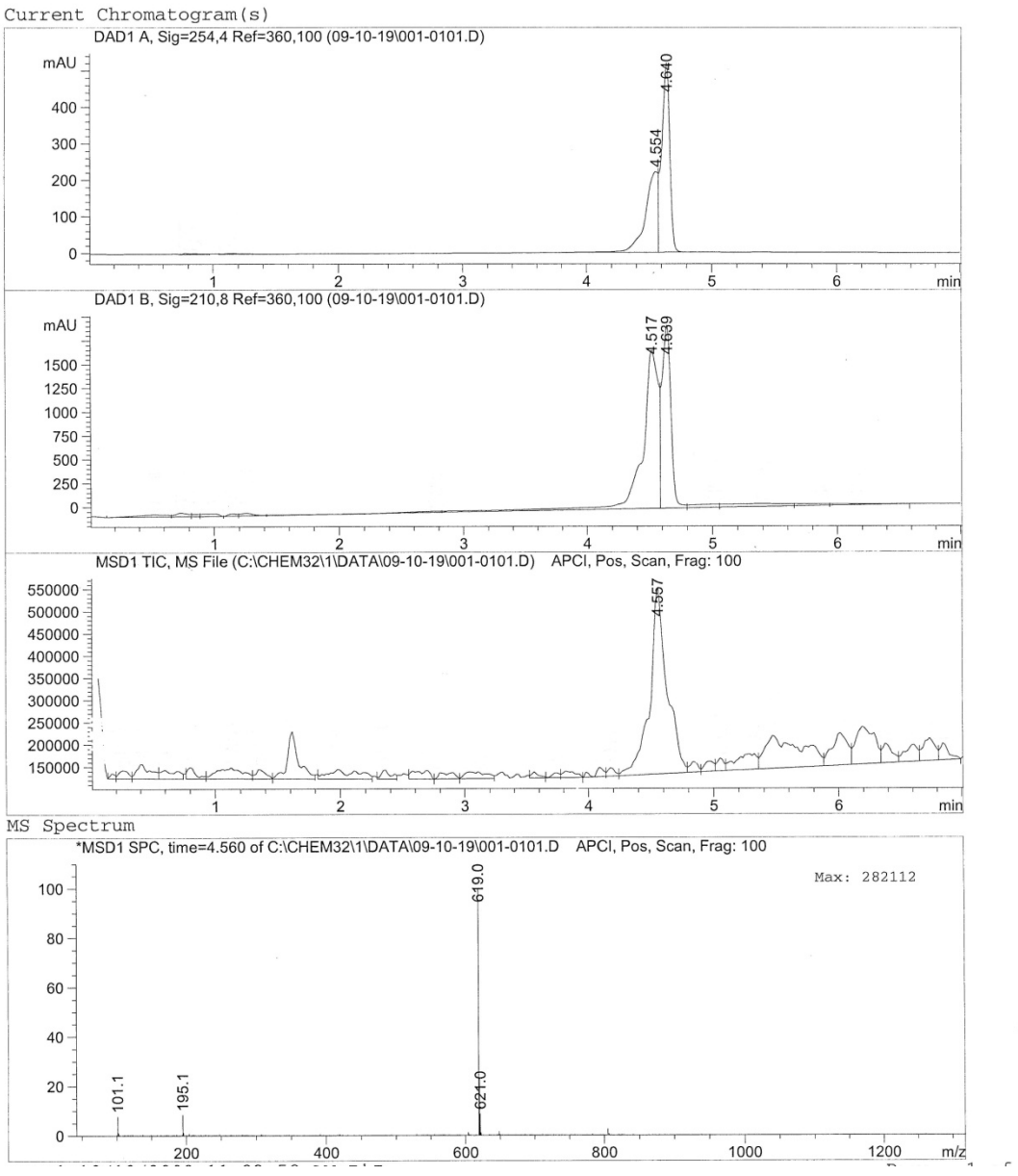



LC-MS (APCI+) m/z 619.

$^{1}$H NMR (300.128 MHz, $CDCl_3$), δ (ppm) 10.05 (s, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.81 (s, 1H), 7.68 (t, *J* = 15.6 Hz, 1H), 7.57 (d, *J* = 9.9 Hz, 1H)


OSO2C8F17
CHO

**Compound 46**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4.554
min
DAD1 B, Sig=210,8 Ref=360,100 (09-10-19\001-0101.D)
mAU
4.517
4.639
min
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min
MS Spectrum
*MSD1 SPC, time=4.560 of C:\CHEM32\1\DATA\09-10-19\001-0101.D APCI, Pos, Scan, Frag: 100
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101.1
195.1
m/z

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GEMINI-300BB "Mighty300"

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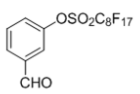
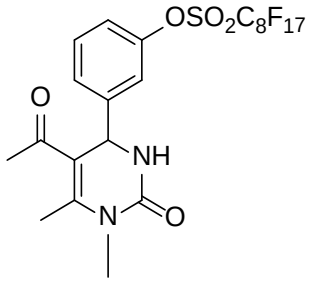



**46**

APPENDIX C

SUPPORTING INFORMATION AND PRODUCT CHARACTERIZATION FOR CHAPTER 3.3

**5-acetyl-4-(3- perfluorooctanesulfonyl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (51):**

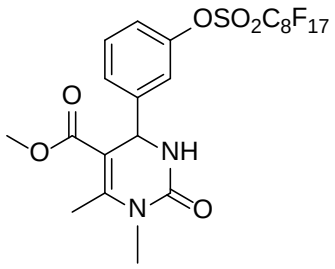



LC-MS (APCI+) *m/z* 743 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.41 (d, *J* = 9.1 Hz, 2H), 7.38 (s, 1H), 7.30 (t, *J* = 13.9Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 3.0 Hz, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 3.23 (s, 3H), 2.47 (s, 3H), 2.23 (s, 3H).

**Methyl 4-(3- perfluorooctanesulfonyl)-1,6-dimethyl-2-oxo-1,2,3,4-**

**tetrahydropyrimidine-5-carboxylate (52):**

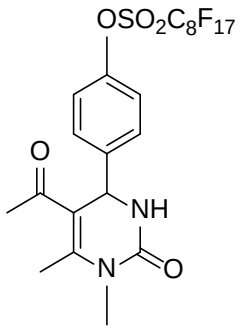



LC-MS (APCI+) *m/z* 759 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.36 (d, *J* = 8.3 Hz, 2H), 7.32 (s, 1H), 7.29 (t, *J* = 13.8 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 3.0 Hz, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 3.68 (s, 3H), 3.23 (s, 3H), 2.46 (s, 3H).

**5-Acetyl-4-(4-perfluorooctanesulfonyl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-**

**one (53):**

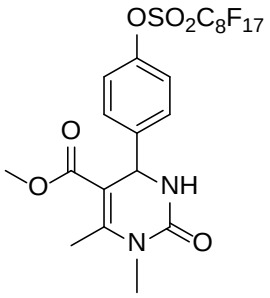



LC-MS (APCI+) *m/z* 743 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 6.27 (d, *J* = 3.0 Hz, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 3.23 (s, 3H), 2.47 (s, 3H), 2.24 (s, 3H).

$^{13}$C NMR (75.5 MHz, $CDCl_3$), δ 195.8, 153.8, 149.3, 148.8, 142.8, 133.6 128.2, 121.9, 121.0 120.3, 119.9, 118.6, 117.4 116.6, 114.8, 113.5, 53.2, 30.6, 29.7, 17.2.

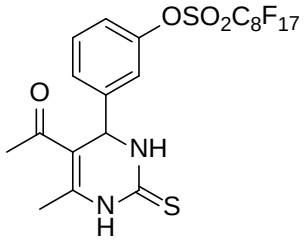
**Methyl 4-(4-perfluorooctanesulfonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (54):**




LC-MS (APCI+) *m/z* 759 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.05 (s, 1H), 5.44 (d, *J* = 3.0 Hz, 1H), 3.68 (s, 3H), 3.23 (s, 3H), 2.58 (s, 3H).

**1-(4-(3-perfluorooctanesulfonyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (56):**

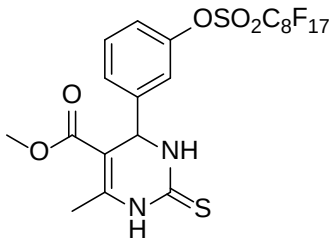



LC-MS (APCI+) *m/z* 745 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), 8.05 (s, 1H), 7.49 (t, *J* = 14.6 Hz, 1H), δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.32 (s, 1H), 7.23 (d, *J* = 7.5Hz, 2H), 6.08 (s, 1H), 2.38 (s, 6H),

**Methyl 4-(3-perfluorooctanesulfonyl)-6-methyl-2-thioxo-1,2,3,4-**

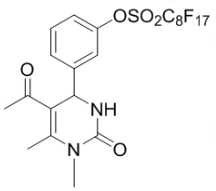
**tetrahydropyrimidine-5-carboxylate (57):**




LC-MS (APCI+) *m/z* 761 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.44 (d, *J* = 9.0 Hz, 2H), 7.38 (s, 1H), 7.22 (t, *J* = 15.3 Hz, 1H), 6.27 (d, *J* = 3.0 Hz, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 3.64 (s, 3H), 2.37 (s, 3H).

**Product 51**

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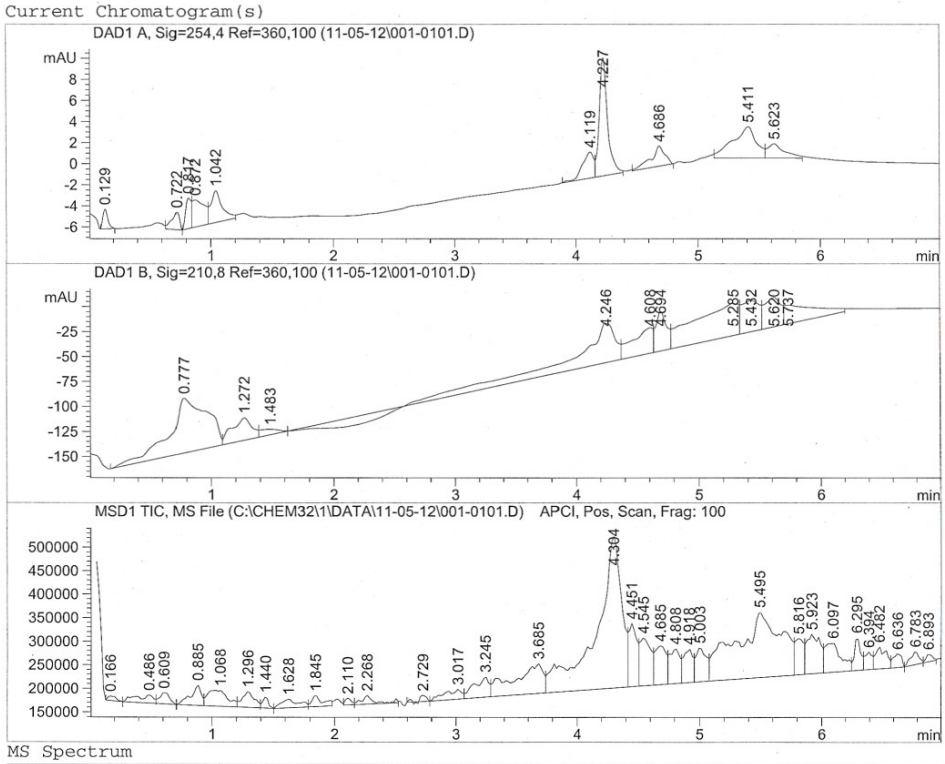


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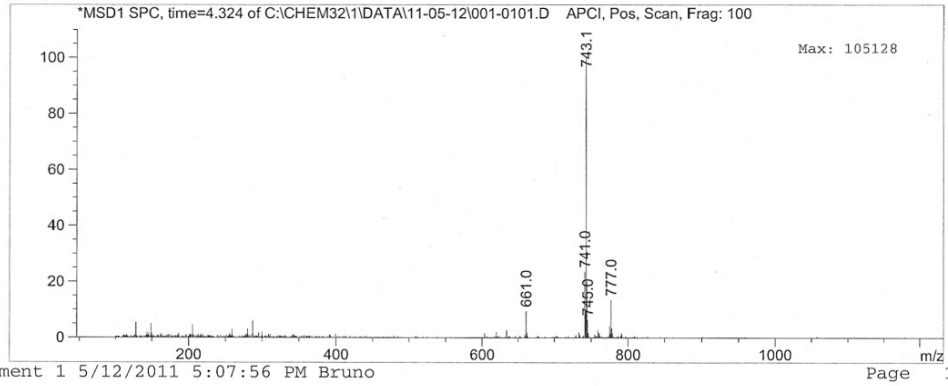

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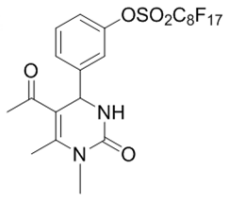


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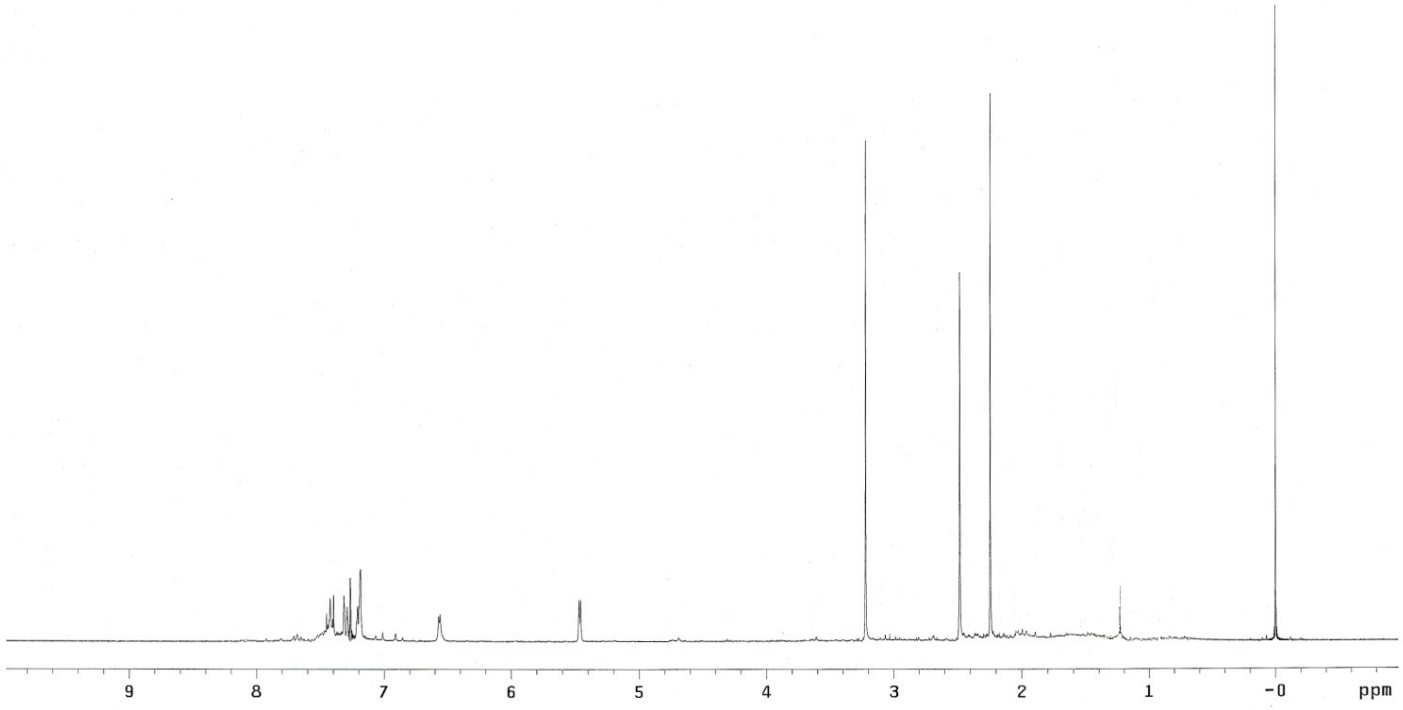

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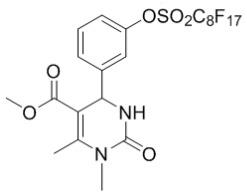


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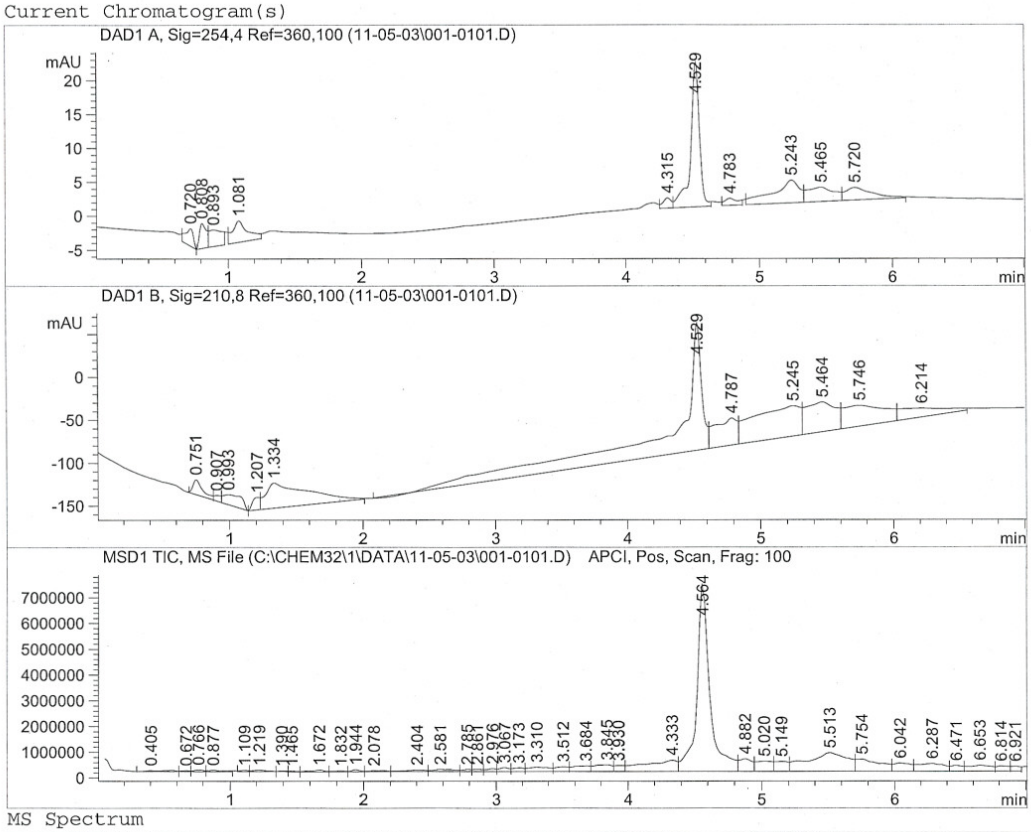


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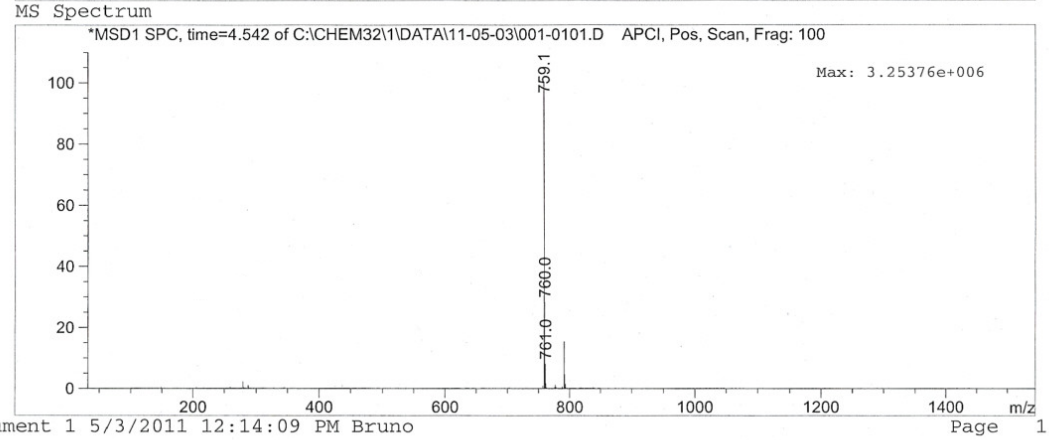

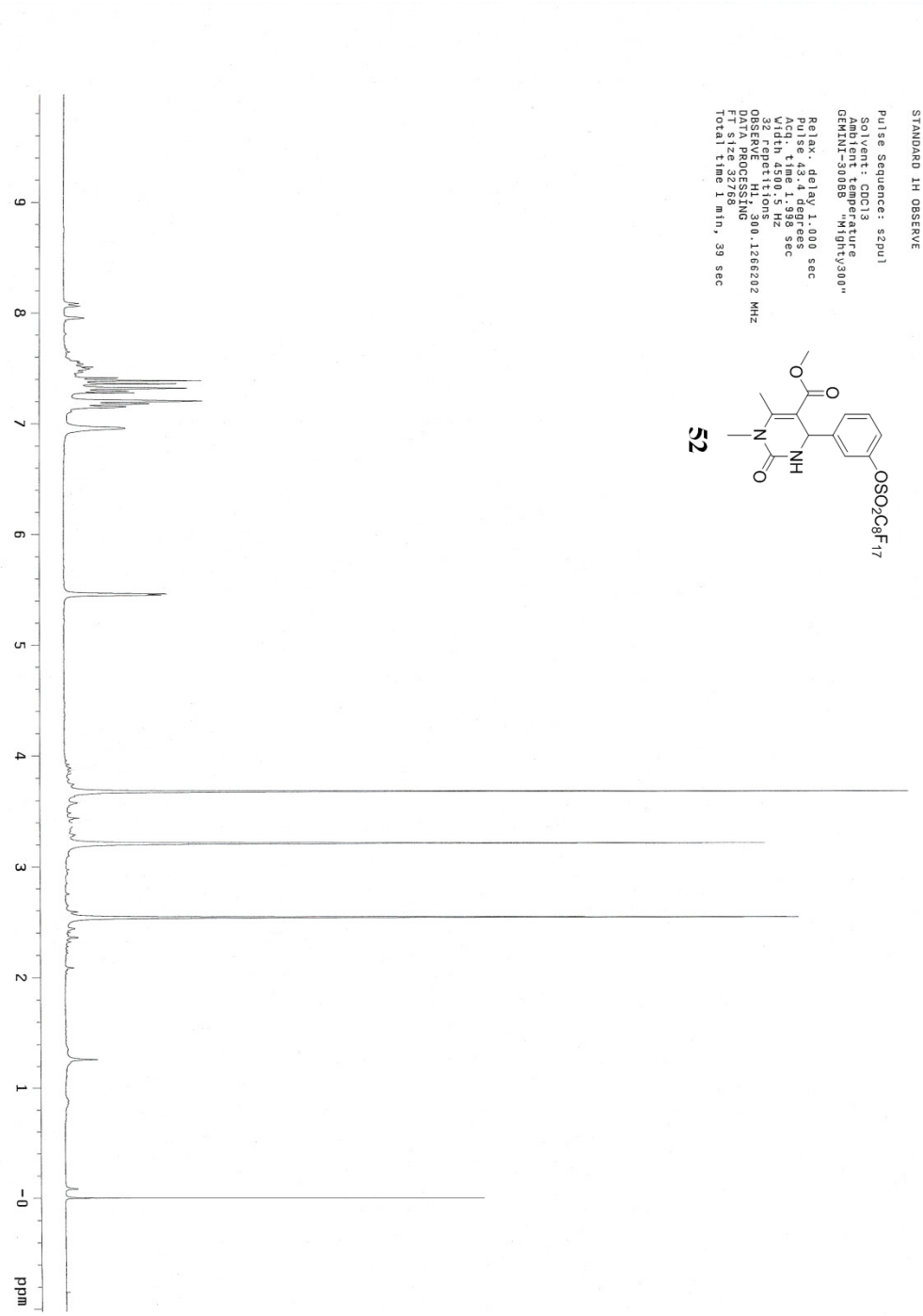
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Pulse 43.4 degrees
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Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266202 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec
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5
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ppm

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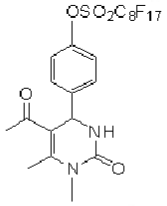


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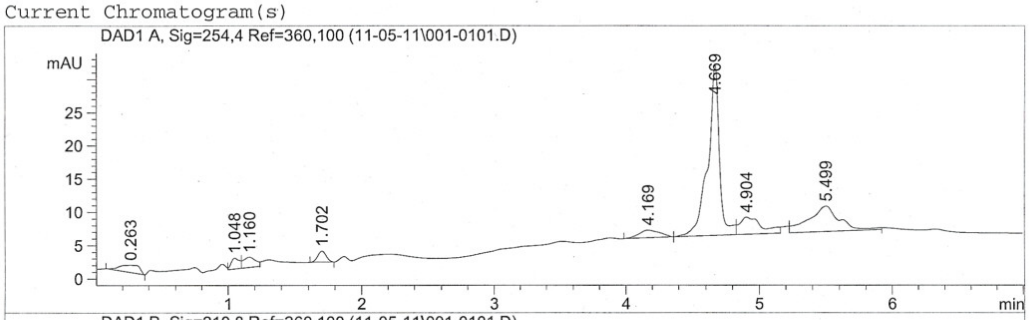
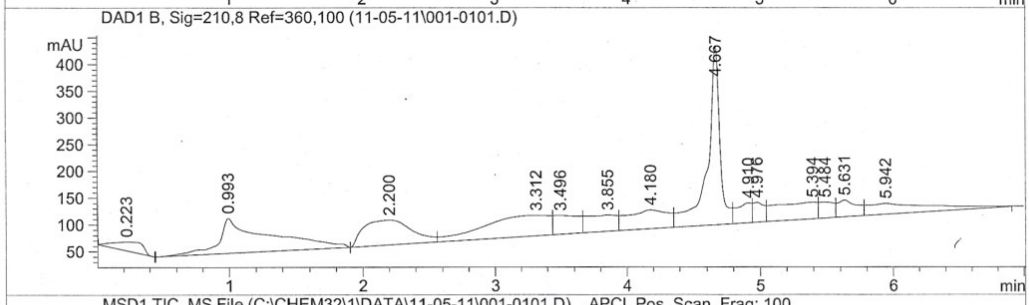
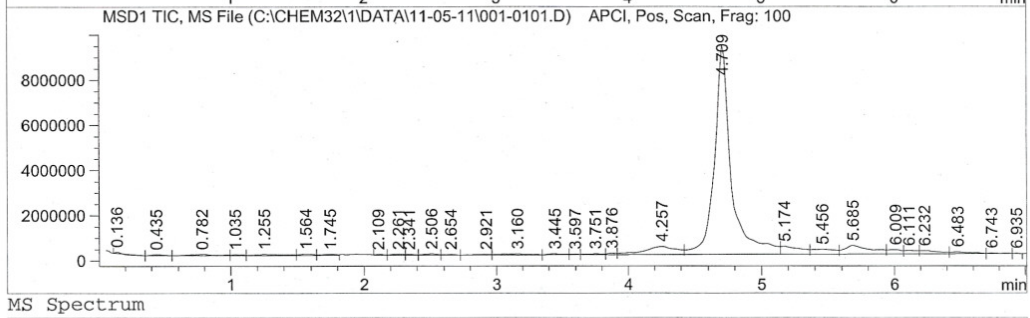
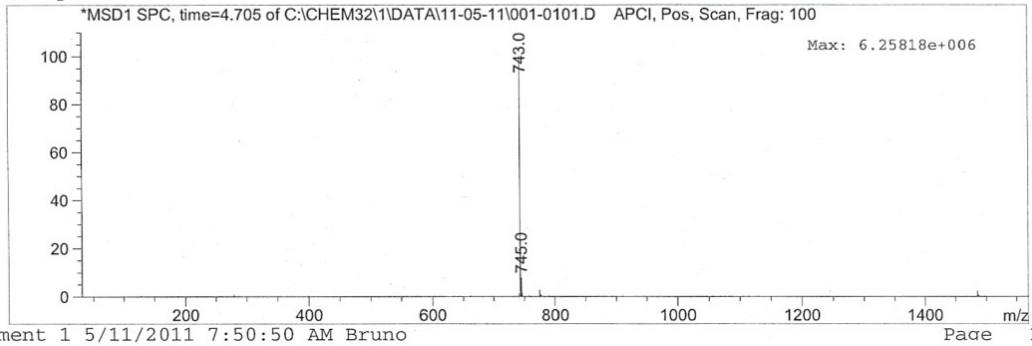


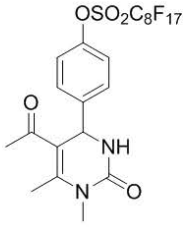

MS Spectrum



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266232 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

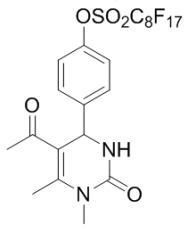



**53**

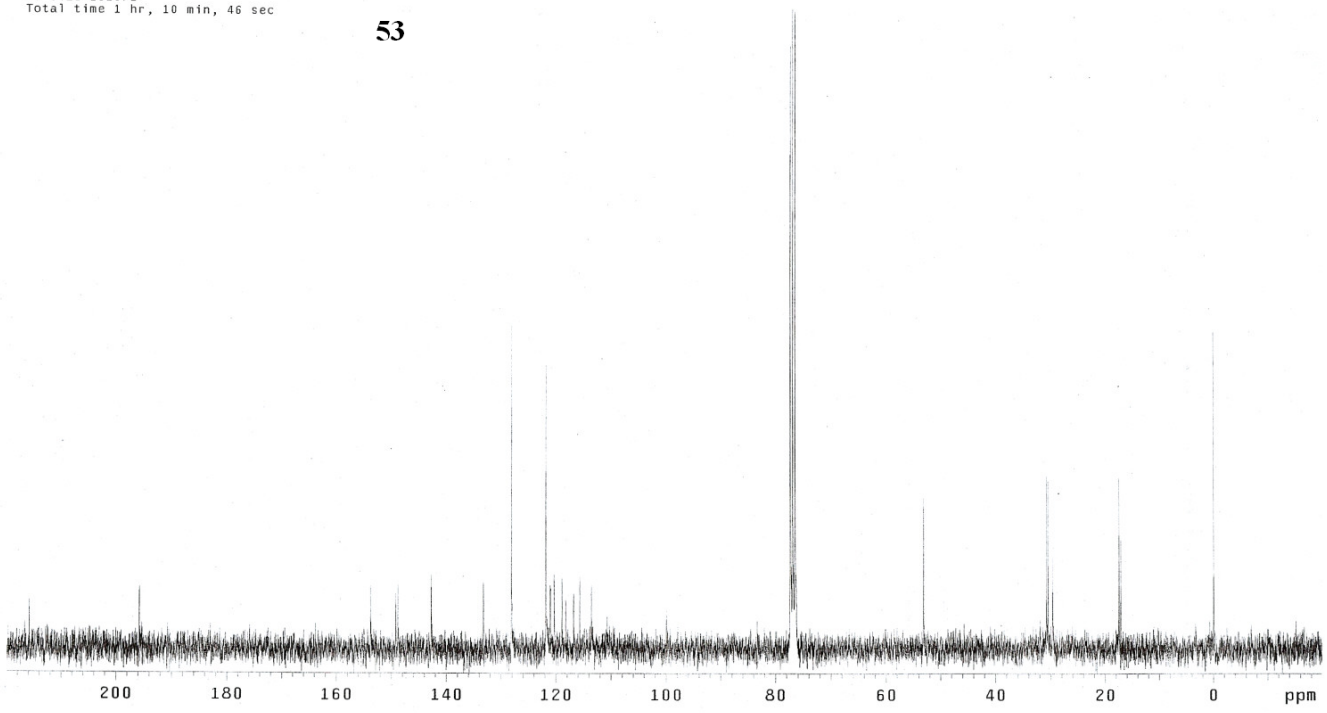
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: A2B3C6-C13
GEMINI-300BB "Mighty300"

Relax. delay 2.000 sec
Pulse 67.8 degrees
Acq. time 1.815 sec
Width 20000.0 Hz
1028 repetitions
OBSERVE C13, 75.4669013 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 10 min, 46 sec




**53**



**Product 54**

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Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-05-03\002-0201.D
Sample Name : A2B1C5
======================================================================
Acq. Operator   : Bruno                          Seq. Line :   2
Acq. Instrument : Instrument 1                    Location : Vial 2
Injection Date  : 5/3/2011 11:22:13 AM               Inj :   1
                                                 Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
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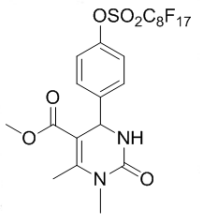
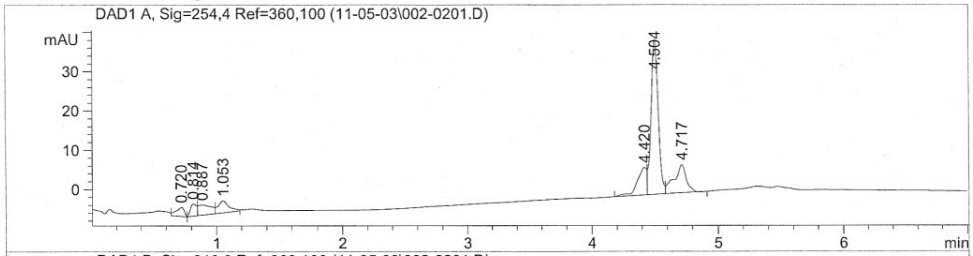
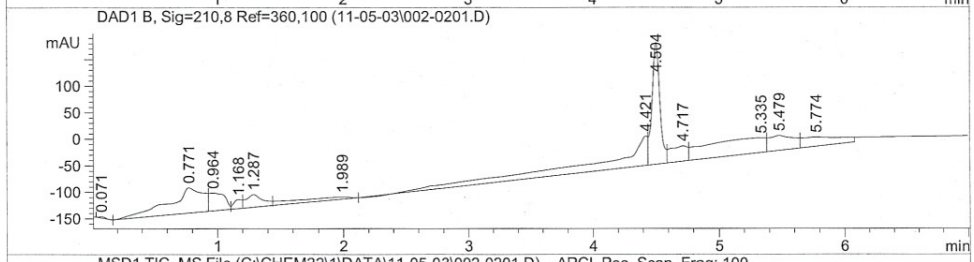
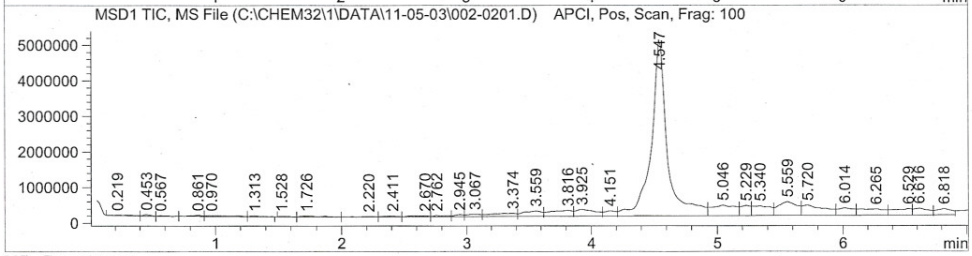


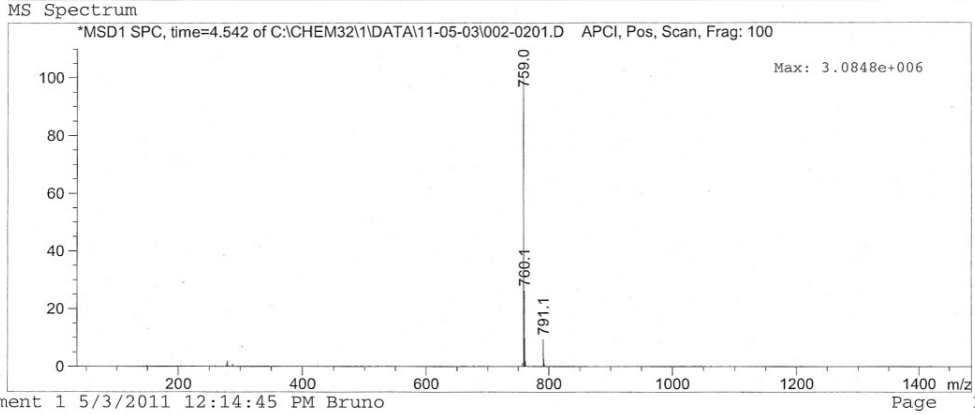

Current Chromatogram(s)



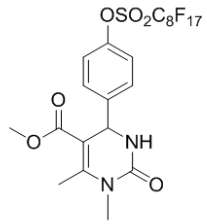

MS Spectrum



STANDARD 1H OBSERVE

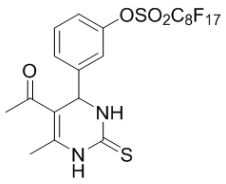
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: A2B3C5
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
256 repetitions
OBSERVE H1, 300.1266235 MHz
DATA PROCESSING
FT size 32768
Total time 13 min, 16 sec




**54**

**Product 56**

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Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-02-01\034-0401.D
Sample Name : A3B1C6 FC Fr-26
==========================================================================
Acq. Operator   : B                                 Seq. Line :   4
     Instrument : Instrument 1                       Location : Vial 34
Injection Date  : 2/1/2010 9:06:28 PM                    Inj :   1
                                                   Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 1/19/2010 4:54:55 PM by  J
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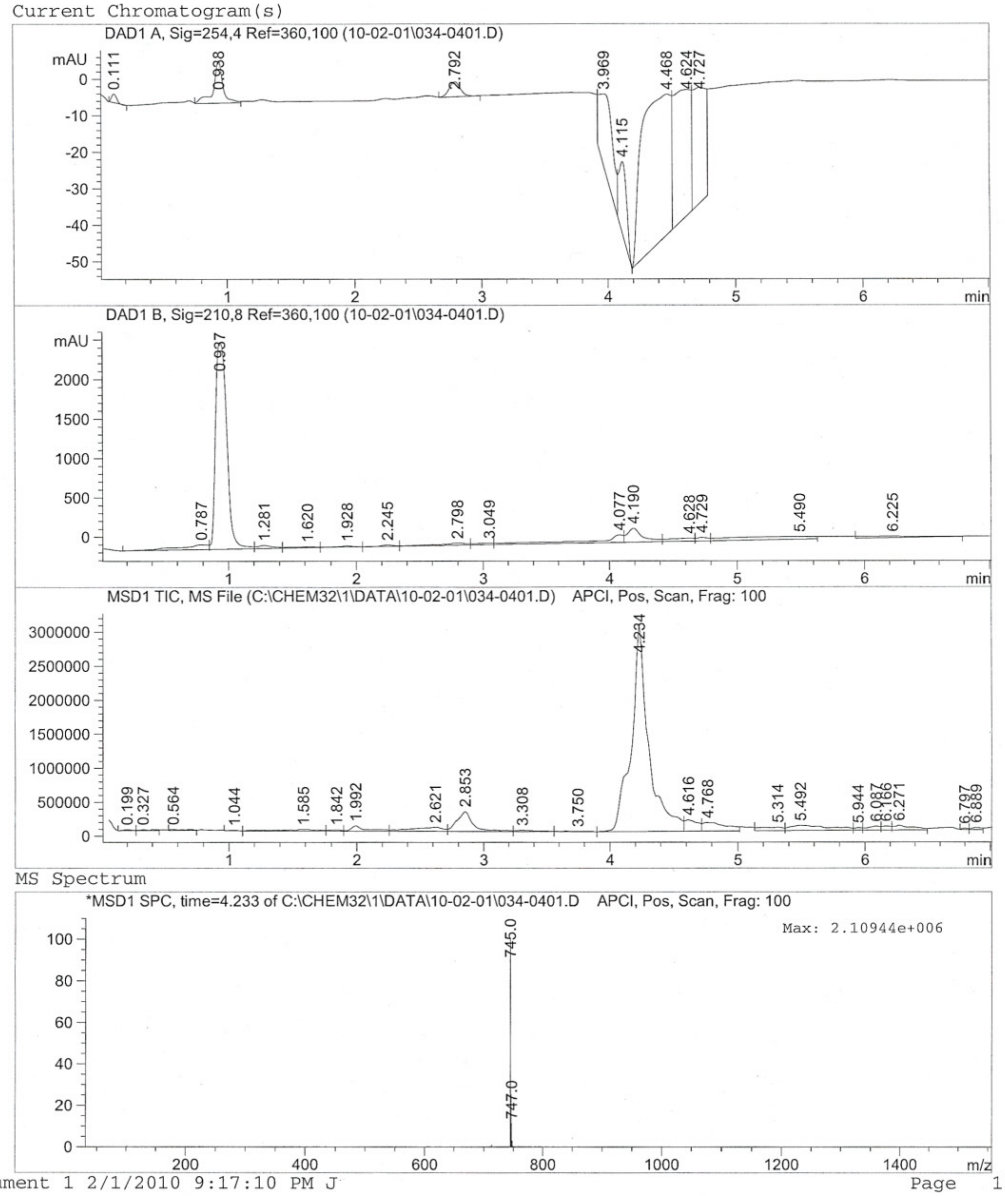
Current Chromatogram(s)

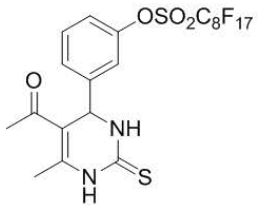



MS Spectrum

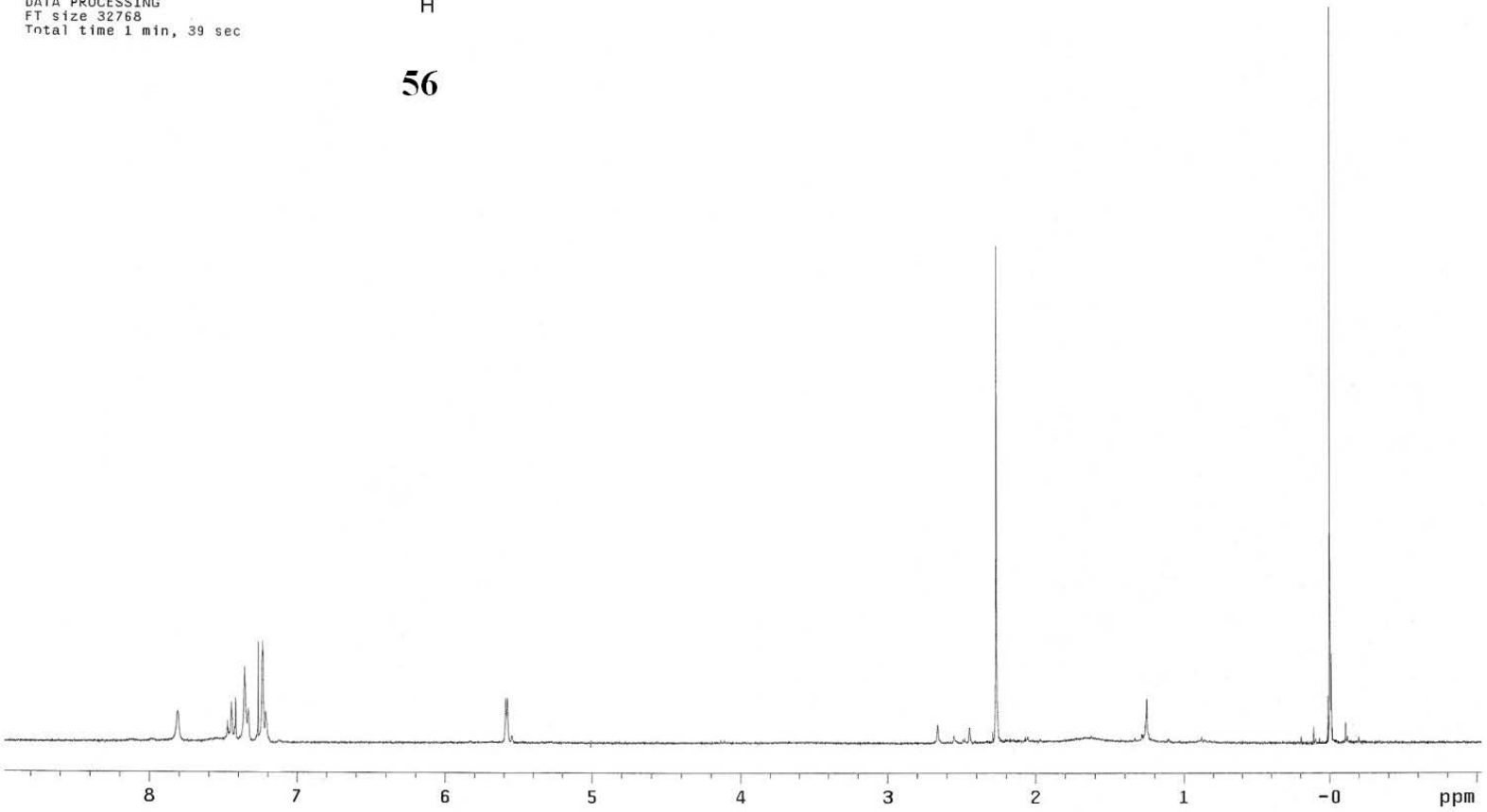
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: A5B1C6-FCY
GEMINI-300BB "Mighty300"

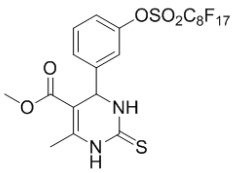
Relax. delay 1.000 sec
Pulse 24.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266232 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec




**56**



**Product 57**

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Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-05-11\005-0101.D
Sample Name : SM
======================================================================
Acq. Operator   : B                          Seq. Line :   1
     Instrument : Instrument 1                Location : Vial 5
Injection Date  : 5/11/2010 6:42:18 PM             Inj :   1
                                           Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/14/2010 4:33:44 PM by J
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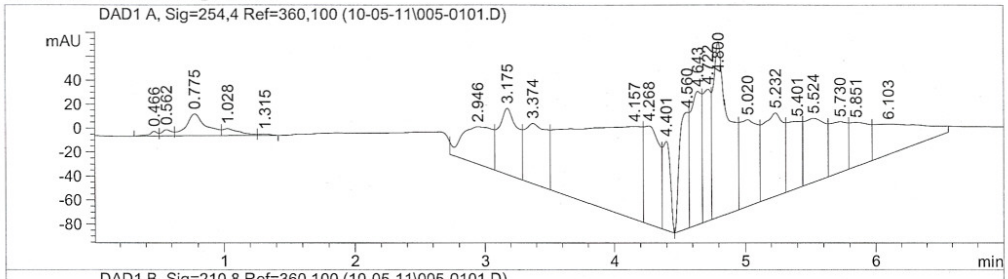
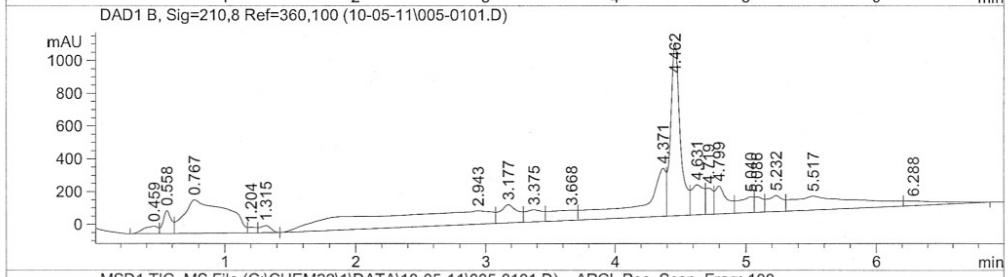
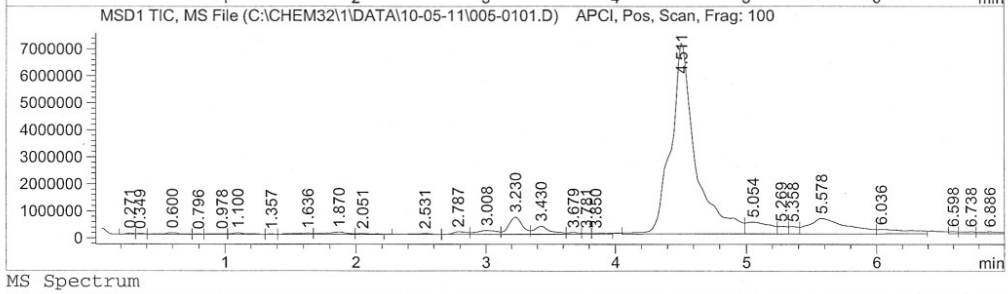
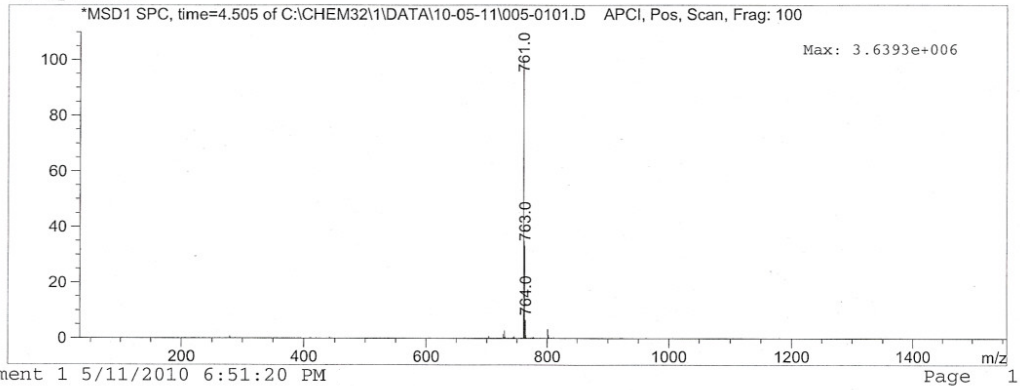
Current Chromatogram(s)



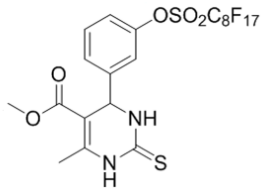

MS Spectrum



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: A5B1C6-FCY
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 24.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266232 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



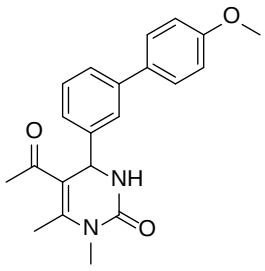

**57**

APPENDIX D

SUPPORTING INFORMATION AND PRODUCT CHARACTERIZATION FOR

CHAPTER 3.4

**5-Acetyl-4-(4'-methoxy-[1,1'-biphenyl]-3-yl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1*H*)-one (60):**

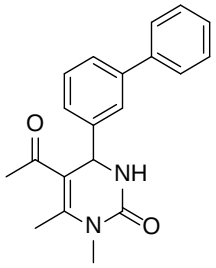



LC-MS (APCI+) *m/z* 351 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.57(d, *J* =12.0 Hz, 2H), 7.49-7.42 (m, 2H), 7.35 (t, *J* = 15.1 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* =12.0 Hz, 2H), 6.03 (d, *J* = 3.0 Hz, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 3.85 (s, 3H), 3.22 (s, 3H), 2.48 (s, 3H), 2.17 (s, 3H).

$^{13}$C NMR (75.5 MHz, $CDCl_3$), δ 196.5, 159.3, 153.6, 148.4, 142.6, 141.7, 133.2, 128.1, 126.6, 124.7, 124.4, 114.3, 113.0, 55.3, 54.6, 30.4, 29.7, 17.1.

**4-([1,1'-biphenyl]-3-yl)-5-acetyl-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (61):**

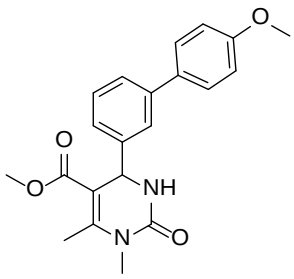



LC-MS (APCI+) *m/z* 321 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 8.16-7.99(m, 2H), 7.44 (d, *J* =15.0 Hz, 2H), 7.37-7.24 (m, 3H), 7.21 (s, 1H), 5.93 (d, *J* = 2.5 Hz, 1H), 5.45 (d, *J* = 2.9 3.22 (s, 3H), 2.48 (s, 3H), 2.23 (s, 3H).

**Methyl 4-(4'-methoxy-[1,1'-biphenyl]-3-yl)-1,6-dimethyl-2-oxo-1,2,3,4-**

**tetrahydropyrimidine-5-carboxylate (62):**

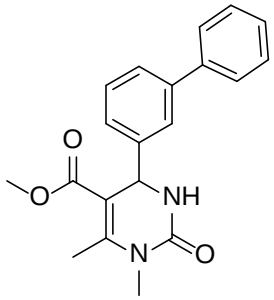



LC-MS (APCI+) *m/z* 367 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.57(d, *J* =11.7 Hz, 1H), 7.49-7.42 (m, 3H), 7.34 (t, *J* = 15.3 Hz, 1H), 7.19-6.95 (m, 2H), 6.76 (s, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 5.45 (d, *J* = 3.0 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.24 (s, 3H), 2.53 (s, 3H).

**Methyl 4-([1,1'-biphenyl]-3-yl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-**

**carboxylate (63):**

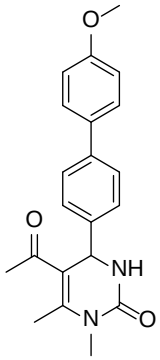


LC-MS (APCI+) *m/z* 337 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ δ 7.53 (t, *J* = 15.9 Hz, 2H), 7.42 (t, *J* = 9.9 Hz, 1H), 7.37-7.29 (m, 5H), 7.24 (s, 1H), 6.09 (d, *J* = 2.7 Hz, 1H), 5.4 (d, *J* = 3.1 Hz, 1H), 3.68 (s, 3H), 3.24 (s, 3H), 2.53 (s, 3H).

$^{13}$C NMR (75.5 MHz, $CDCl_3$), δ 166.5, 154.2, 149.7, 142.1, 140.6, 140.5 128.8, 128.7, 127.4, 127.3, 126.9, 126.5, 103.9, 53.2, 51.3, 30.4, 29.6, 16.6.

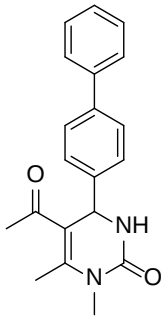
**5-Acetyl-4-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (64):**



LC-MS (APCI+) *m/z* 351 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.58(d, *J* =11.7 Hz, 2H), 7.47-7.41 (m, 4H), 7.36 (d, *J* = 9.0 Hz, 2H), 5.68 (d, *J* = 2.5 Hz, 1H), 5.44 (d, *J* = 2.9 Hz, 1H), 3.85 (s, 3H), 3.25 (s, 3H), 2.57 (s, 3H), 2.16 (s, 3H)

**4-([1,1'-biphenyl]-4-yl)-5-acetyl-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (65):**

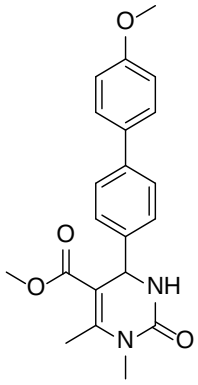



LC-MS (APCI+) *m/z* 321 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.57(d, *J* =10.1 Hz, 4H), 7.43 (t, *J* = 15.7 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.29 (d, J =9.0 Hz, 2H), 6.08 (s, 1H), 5.43 (s, 1H), 3.23 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H).

**Methyl 4-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1,6-dimethyl-2-oxo-1,2,3,4**

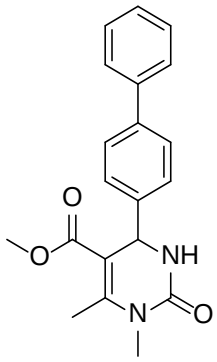
**tetrahydropyrimidine-5-carboxylate (66):**




LC-MS (APCI+) *m/z* 367 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.56 (d, *J* =12.0 Hz, 2H), 7.33-7.26 (m, 4H), 6.96 (d *J* = 9.0 Hz, 2H), 5.71 (d, *J* = 2.1 Hz, 1H), 5.45 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H), 3.68(s, 3H), 2.55 (s, 3H),

**Methyl 4-([1,1'-biphenyl]-4-yl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (67):**

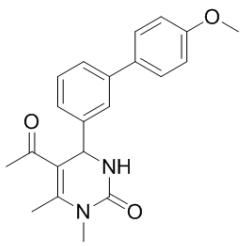



LC-MS (APCI+) *m/z* 337 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.53 (t, *J* = 16.2 Hz, 2H), 7.35 (t, *J* = 10.2 Hz, 1H), 7.38-7.29 (m, 6H), 6.23 (d, *J* = 2.7 Hz, 1H), 5.4 (d, *J* = 3.1 Hz, 1H), 3.68 (s, 3H), 3.23 (s, 3H), 2.53 (s, 3H).

$^{13}$C NMR (75.5 MHz, $CDCl_3$), δ 199.5, 166.5, 154.2, 149.7, 142.1, 140.7, 140.5 128.8, 128.7, 127.4, 127.3, 126.9, 126.5, 103.9, 53.2, 51.3, 30.4, 16.6.

**Product 60**



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Sample Name : A2B1C6D1
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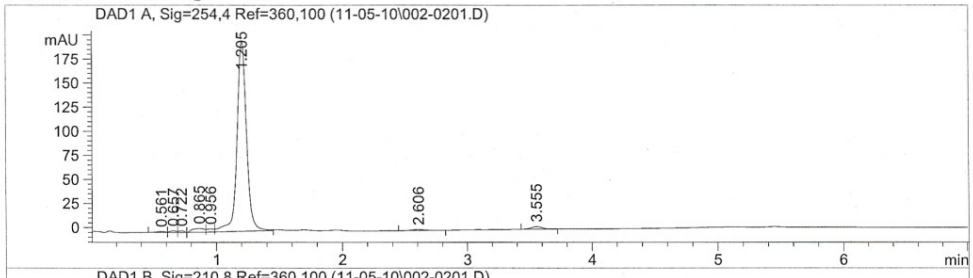
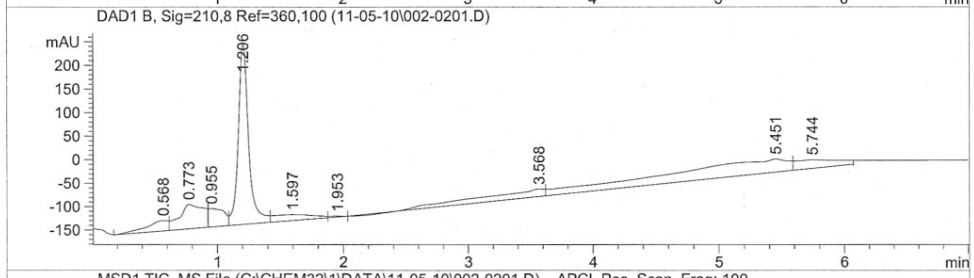
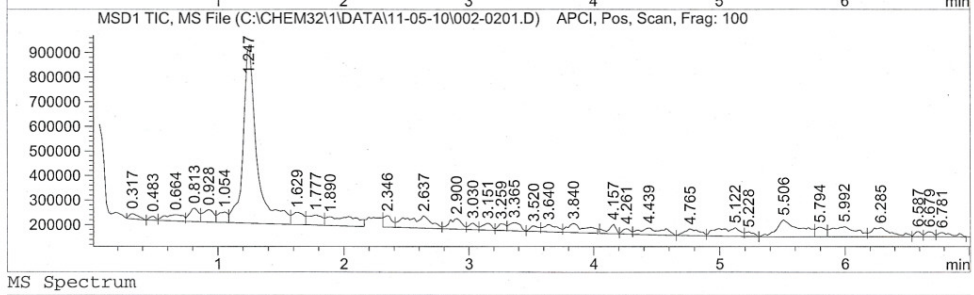
Acq. Instrument : Instrument 1                        Location : Vial 2
Injection Date  : 5/10/2011 12:05:57 PM                    Inj :   1
                                                    Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
```

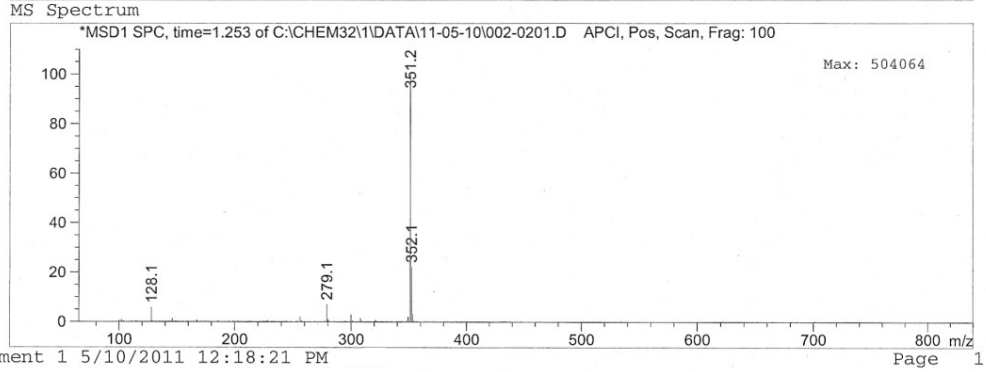
Current Chromatogram(s)



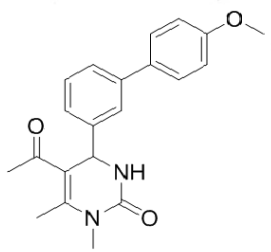

MS Spectrum



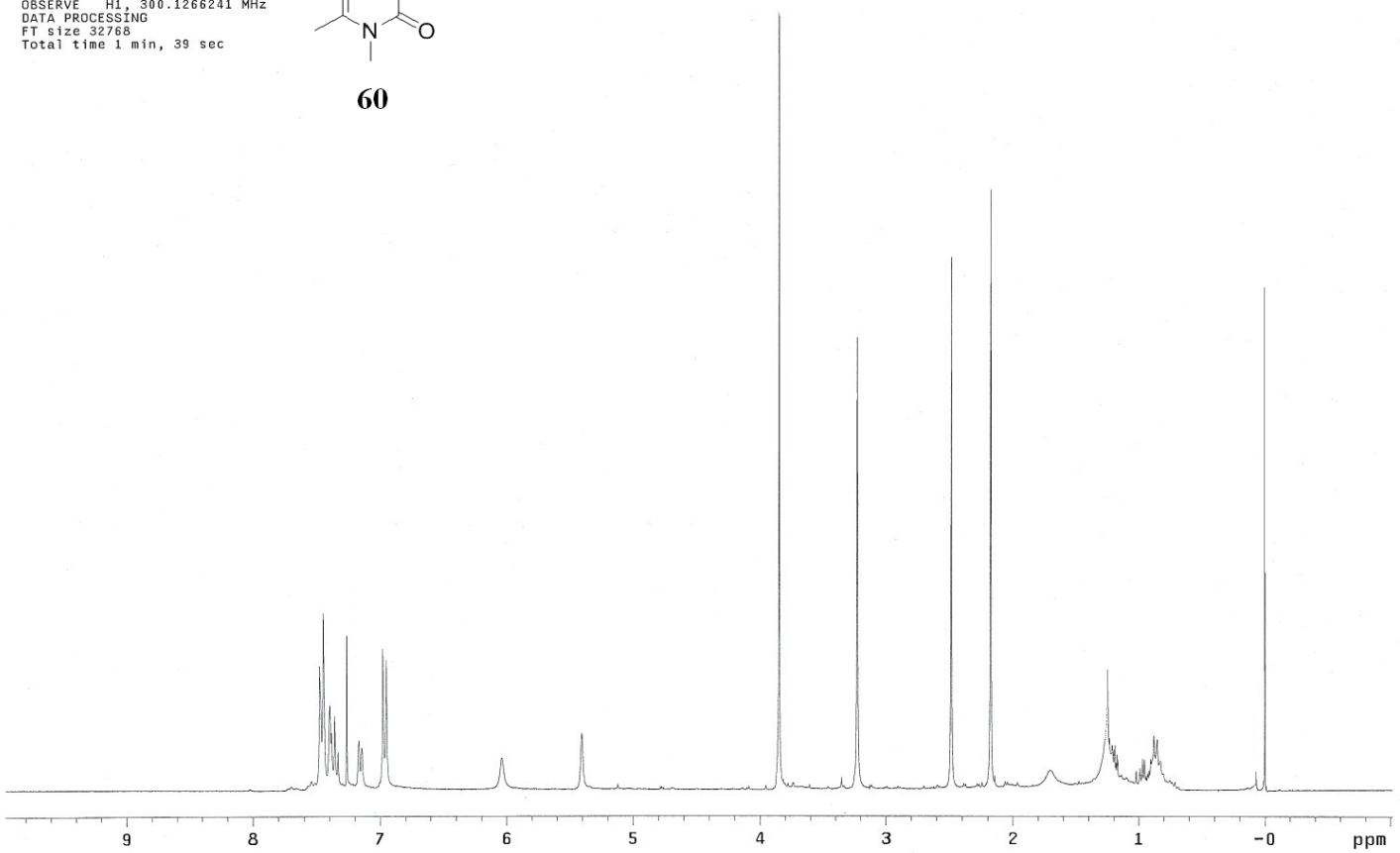
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266241 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



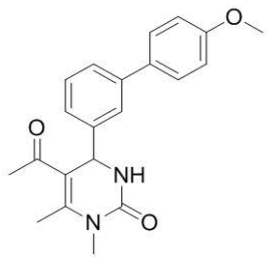

**60**



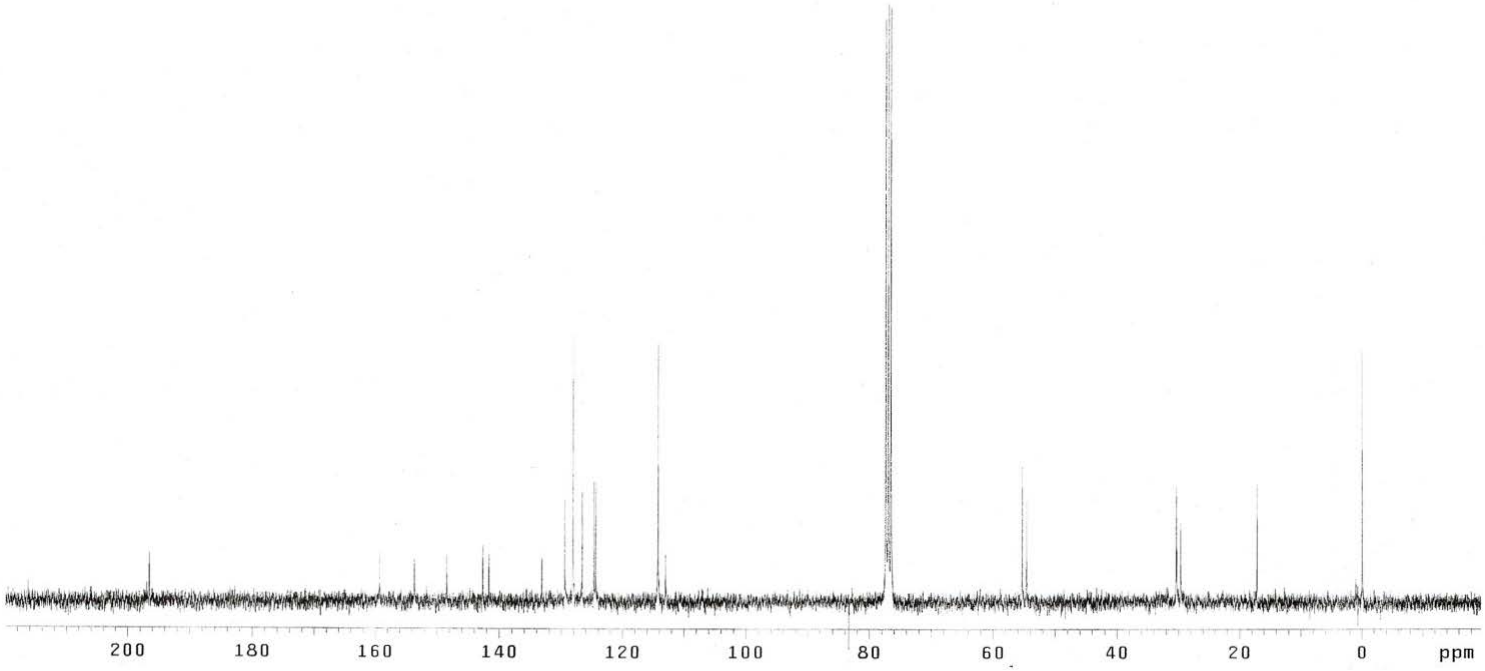
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

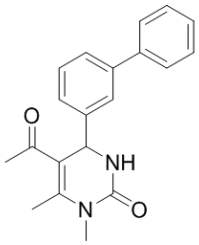
Relax. delay 2.000 sec
Pulse 67.8 degrees
Acq. time 1.815 sec
Width 20000.0 Hz
1028 repetitions
OBSERVE C13, 75.4669007 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 10 min, 46 sec




**60**

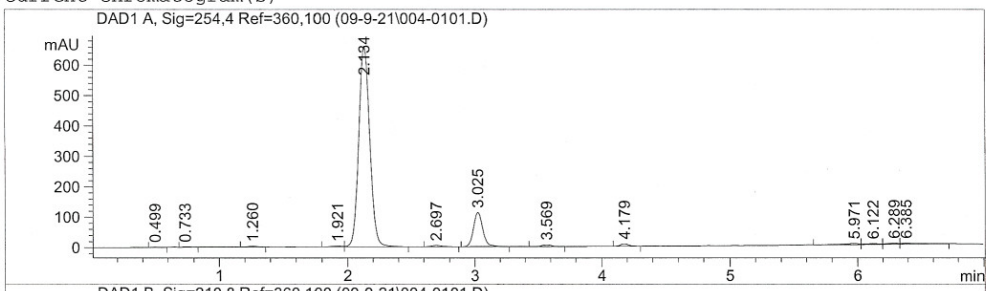


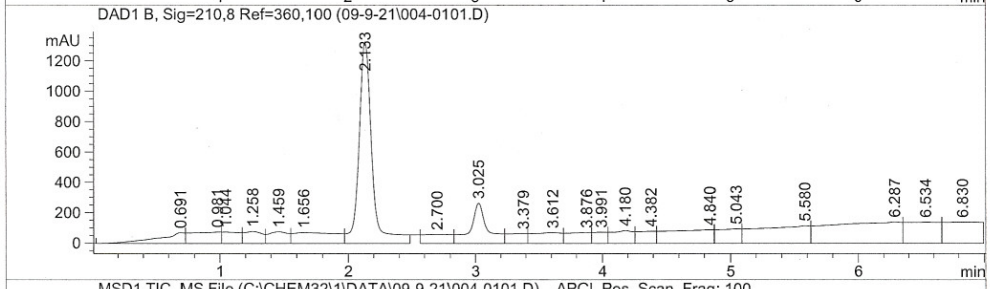
**Product 61**

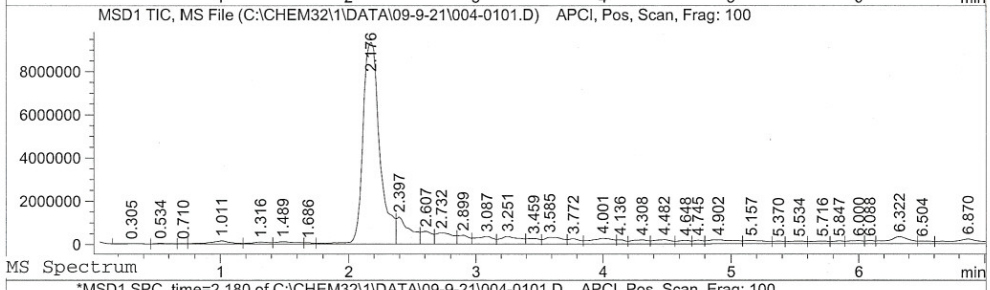



```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\09-9-21\004-0101.D
Sample Name : A2B1C6+D2
==========================================================================
Acq. Operator   : B                                 Seq. Line :   1
A    Instrument : Instrument 1                       Location : Vial 4
Injection Date  : 9/22/2009 9:39:07 PM                   Inj :   1
                                                   Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 9/1/2009 1:16:42 PM by J
```

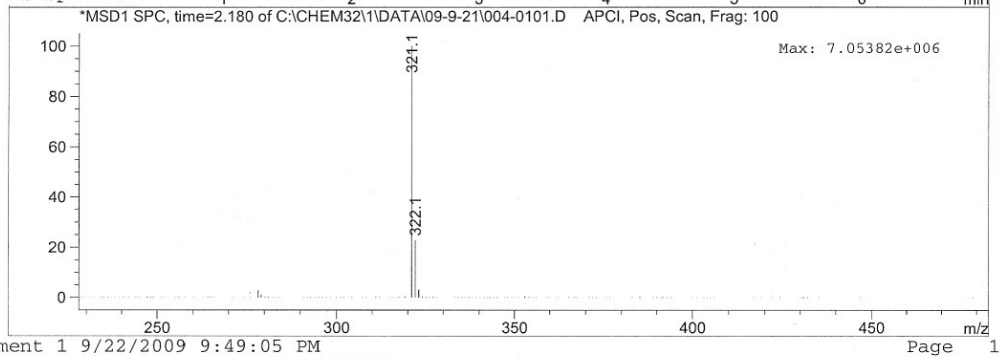
Current Chromatogram(s)



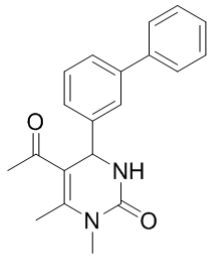

MS Spectrum



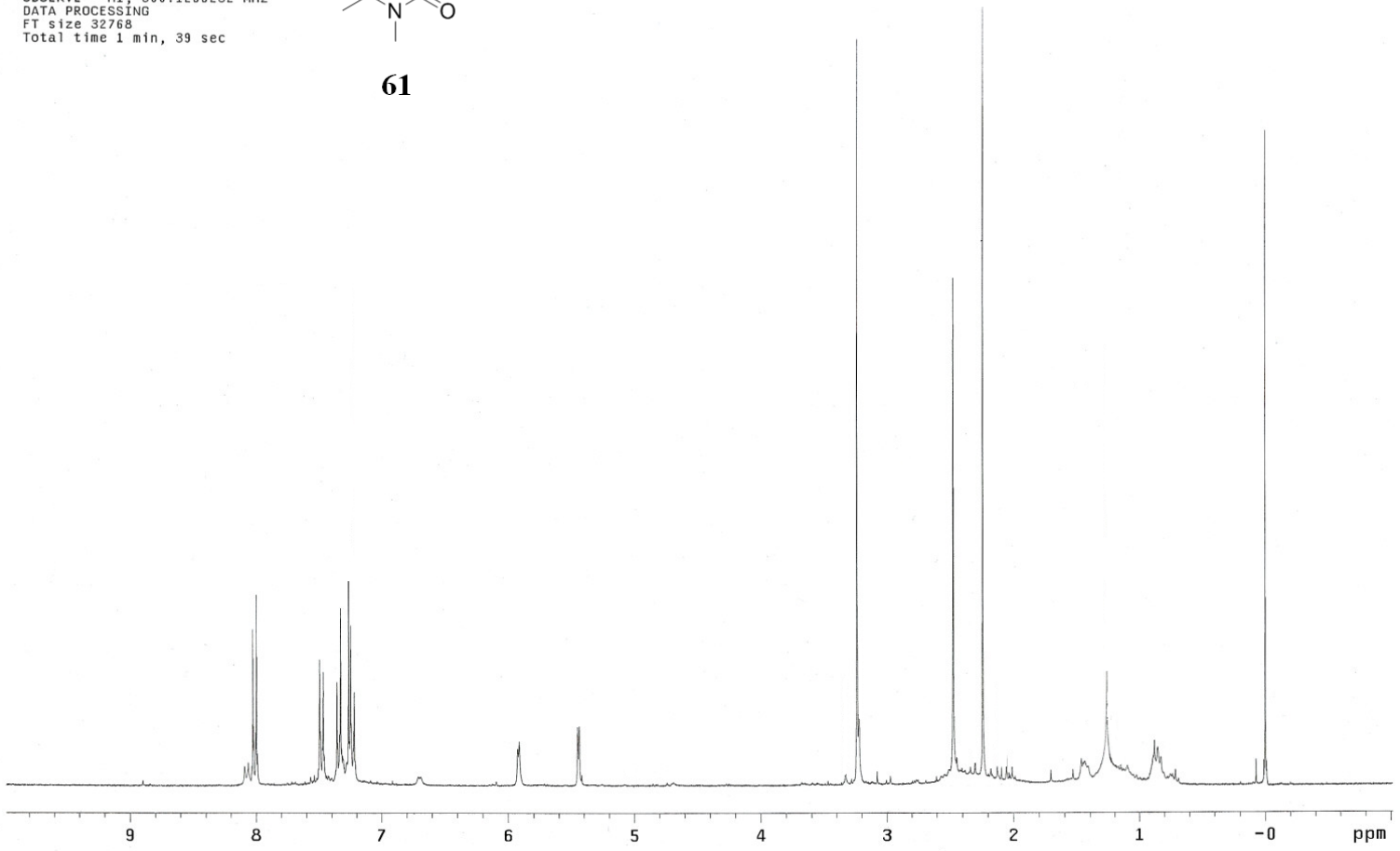
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

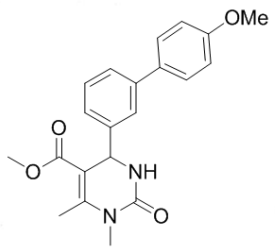
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266232 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec




**61**

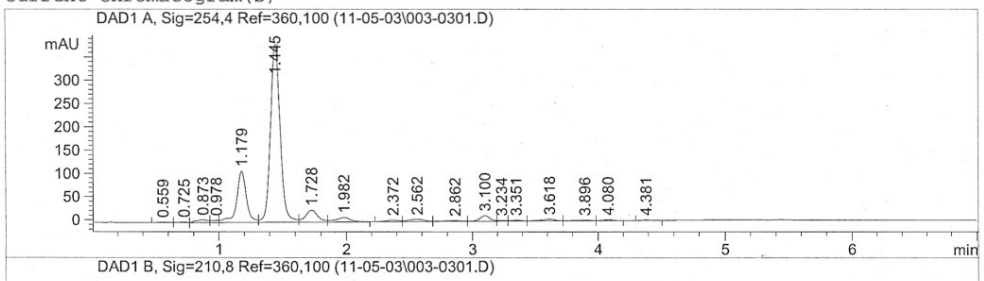


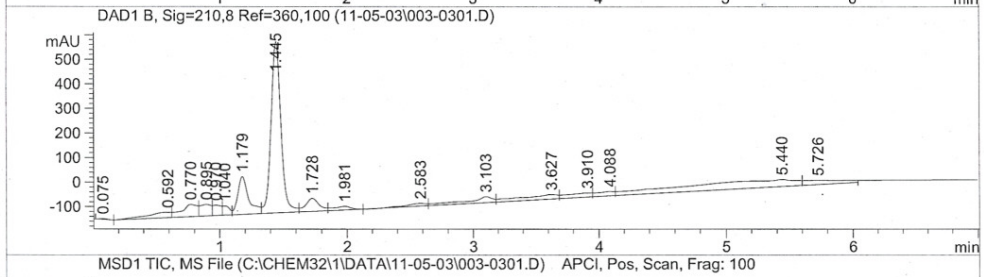
**Product 62**

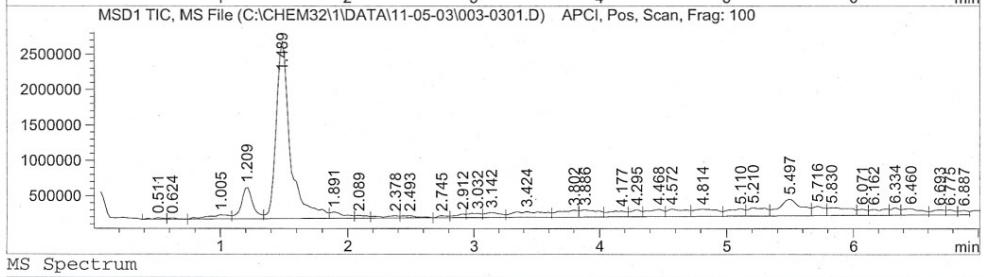



```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-05-03\003-0301.D
Sample Name : A2B1B5D1
======================================================================
Acq. Operator   : B                              Seq. Line :   3
Acq. Instrument : Instrument 1                    Location : Vial 3
Injection Date  : 5/3/2011 11:30:47 AM                Inj :   1
                                                 Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
```

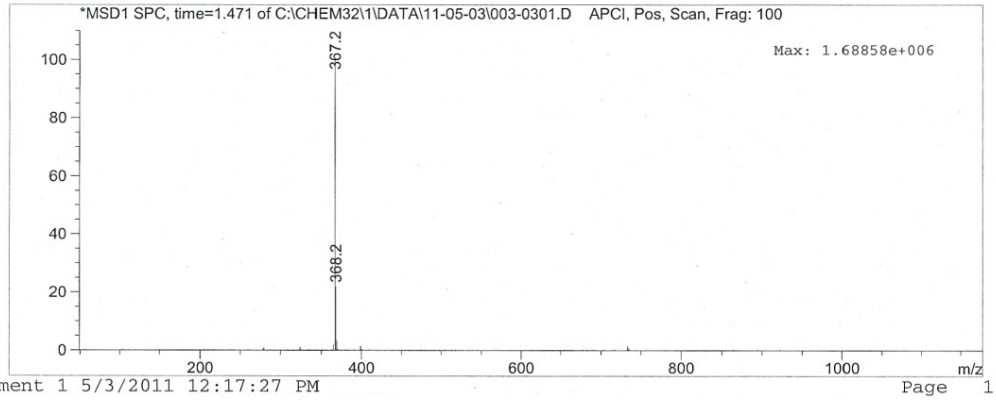
Current Chromatogram(s)



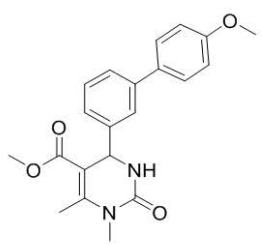

MS Spectrum



STANDARD 1H OBSERVE

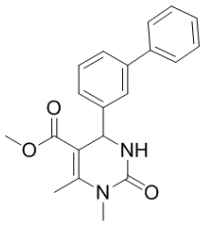
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266208 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec



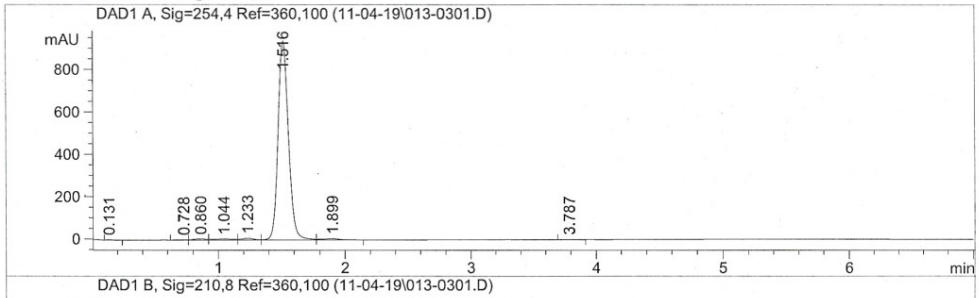

**62**

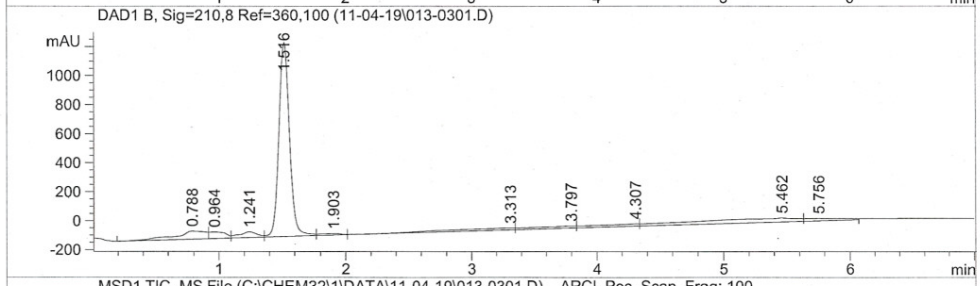
**Product 63**

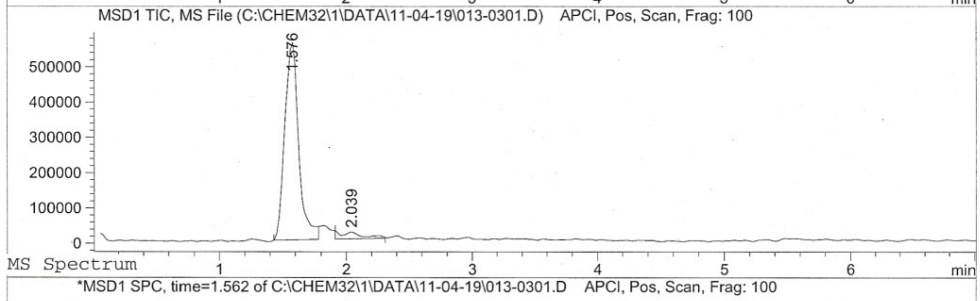


```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-04-19\013-0301.D
Sample Name : A2B1C5D2
========================================================================
Acq. Operator   : B                                  Seq. Line :   3
Acq. Instrument : Instrument 1                        Location : Vial 13
Injection Date  : 4/19/2011 2:39:19 PM                    Inj :   1
                                                    Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 3/10/2011 9:35:54 PM by Z
```

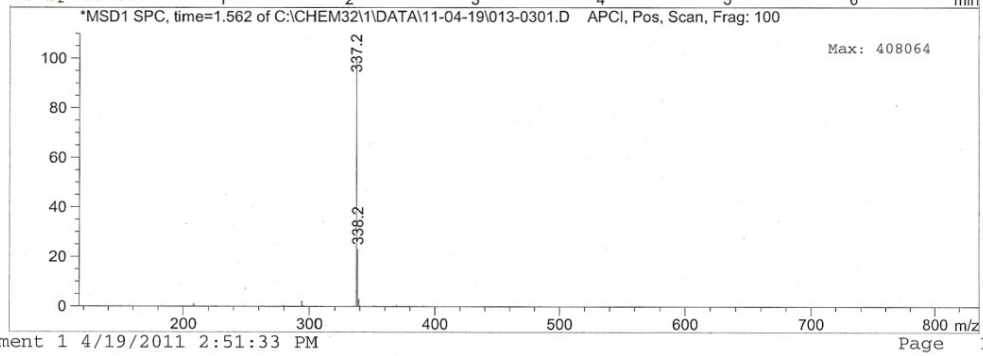
Current Chromatogram(s)

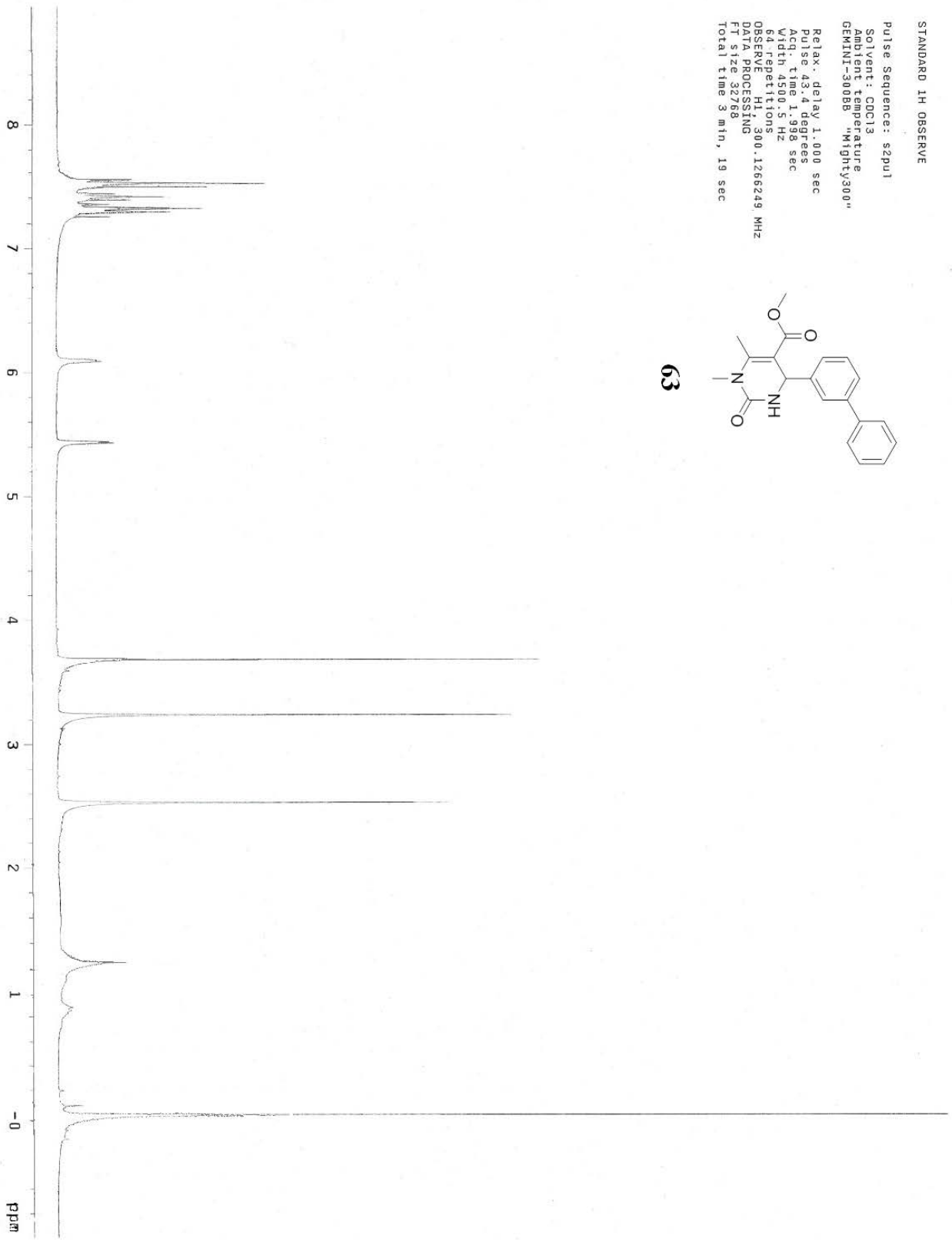



MS Spectrum

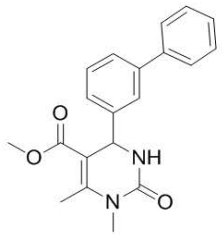



STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266249 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 19 sec
63
8
7
6
5
4
3
2
1
-0
ppm

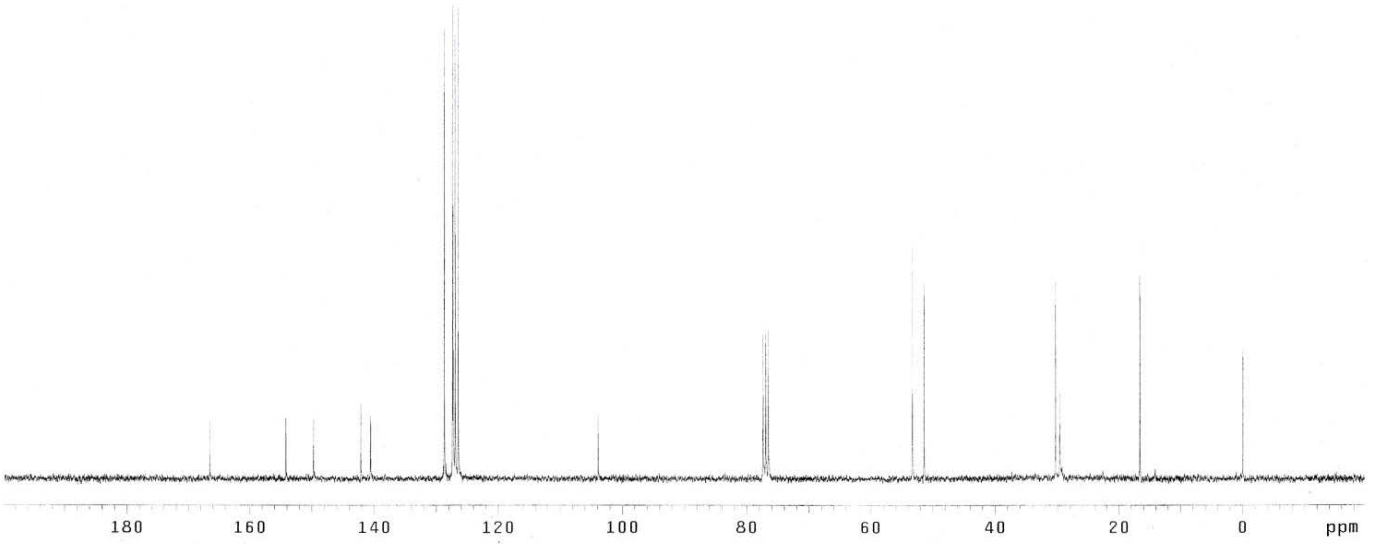
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: C13A2B1C5D2
GEMINI-300BB "Mighty300"

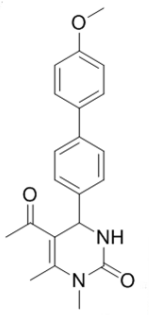
Pulse 67.8 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
2048 repetitions
OBSERVE C13, 75.4669036 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 12 min, 7 sec




**63**



**Product 64**

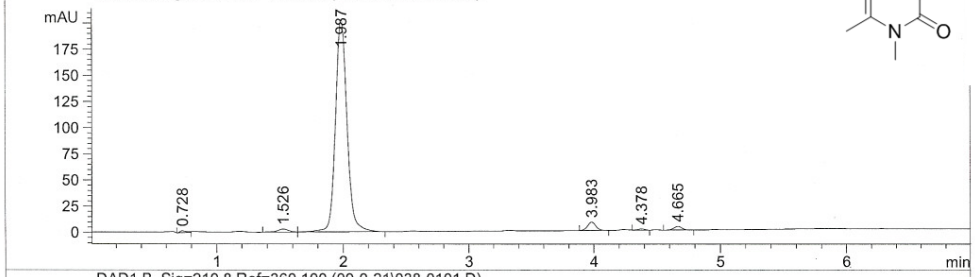



rint of all graphic windows
Data File : C:\CHEM32\1\DATA\09-9-21\038-0101.D
Sample Name : A2B3C6+D1 Suz

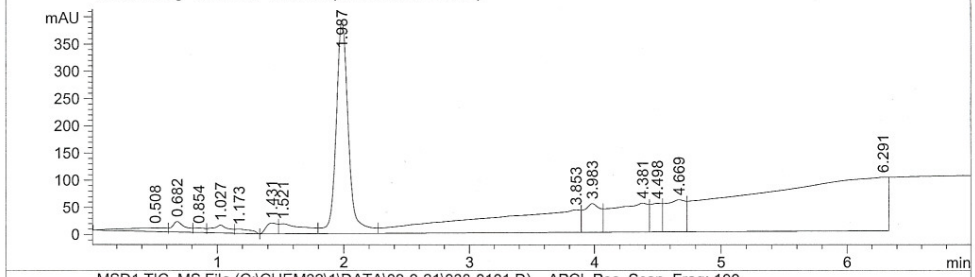
Acq. Operator : B
A Instrument : Instrument 1
Injection Date : 9/21/2009 8:00:43 PM
Seq. Line : 1
Location : Vial 8
Inj : 1
Inj Volume : 4 µl
Method : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed : 9/1/2009 1:16:42 PM by J

Current Chromatogram(s)

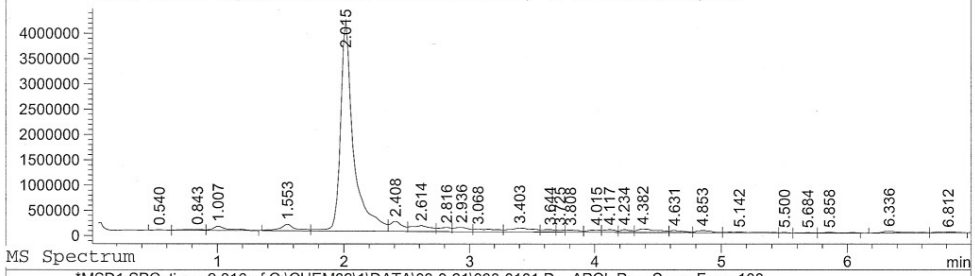
DAD1 A, Sig=254,4 Ref=360,100 (09-9-21\038-0101.D)




DAD1 B, Sig=210,8 Ref=360,100 (09-9-21\038-0101.D)

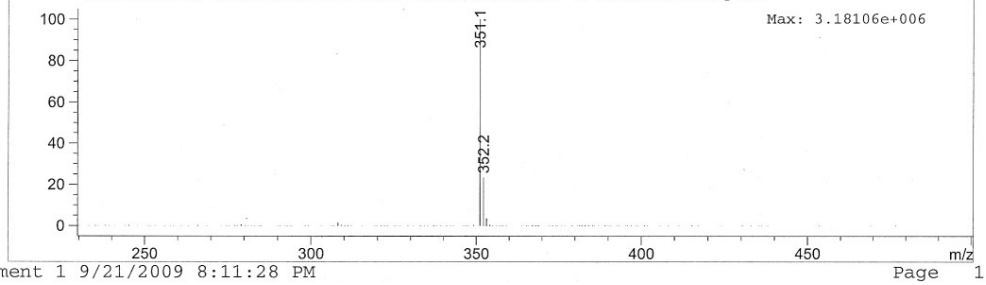



MSD1 TIC, MS File (C:\CHEM32\1\DATA\09-9-21\038-0101.D) APCI, Pos, Scan, Frag: 100




MS Spectrum

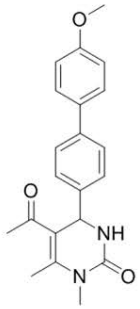
*MSD1 SPC, time=2.016 of C:\CHEM32\1\DATA\09-9-21\038-0101.D APCI, Pos, Scan, Frag: 100



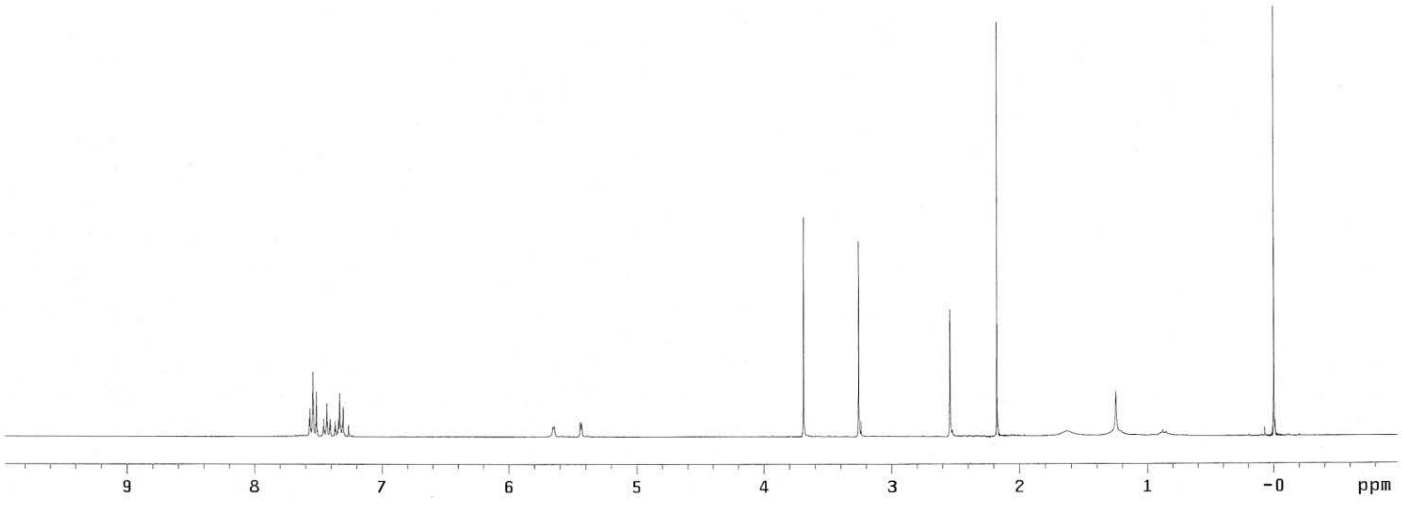
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

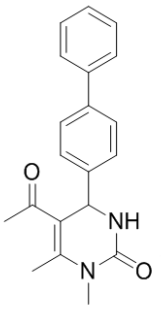
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266238 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec




**64**

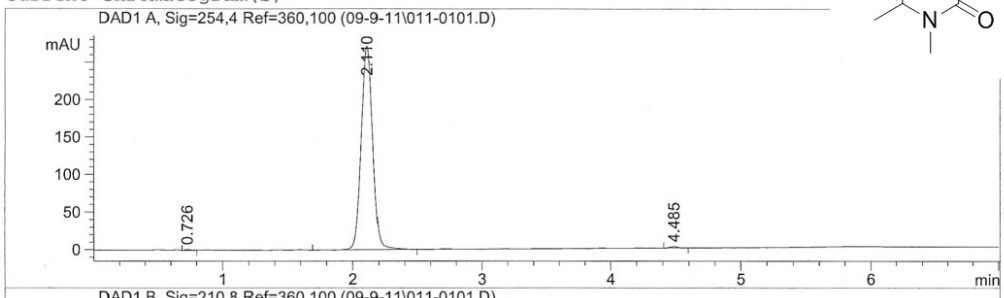


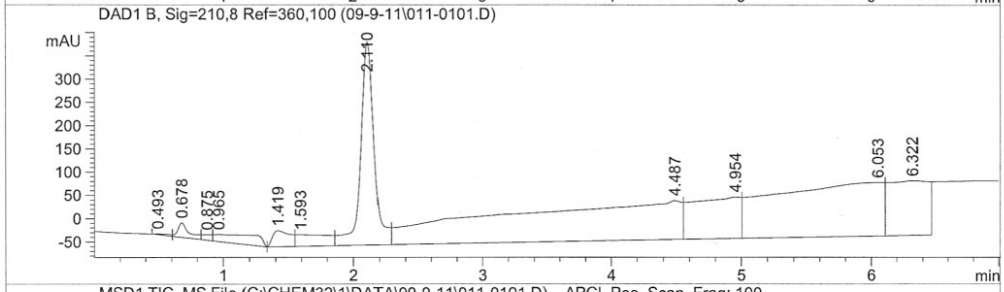
**Product 65**

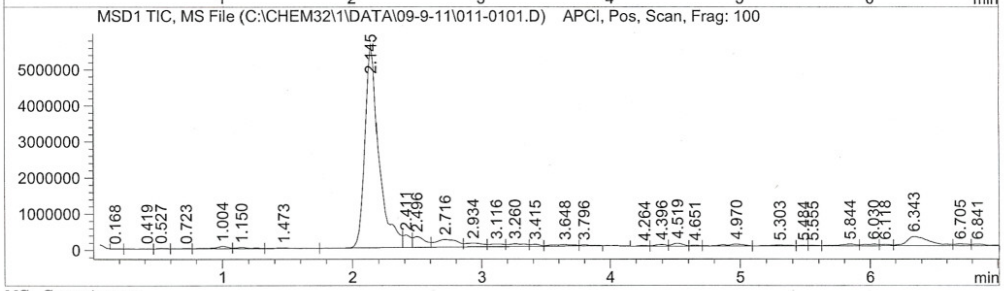



```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\09-9-11\011-0101.D
Sample Name : A2B3C6+D2
======================================================================
Acq. Operator   : B                          Seq. Line :   1
     Instrument : Instrument 1                Location : Vial 11
Injection Date  : 9/11/2009 5:41:07 PM             Inj :   1
                                            Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 9/1/2009 1:16:42 PM by J
```

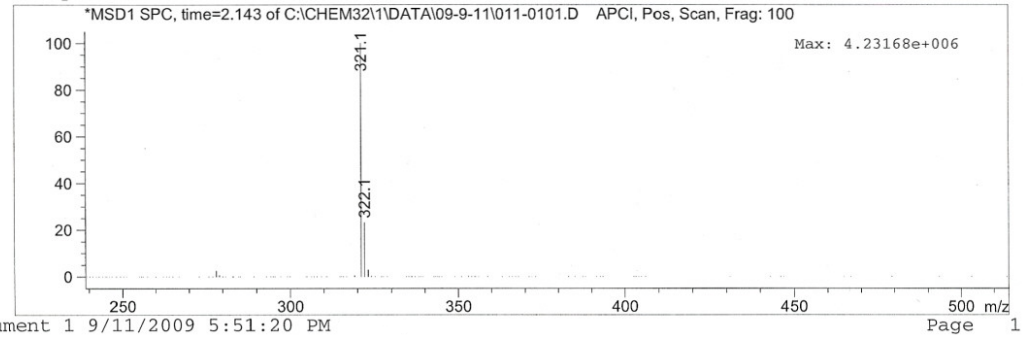
Current Chromatogram(s)

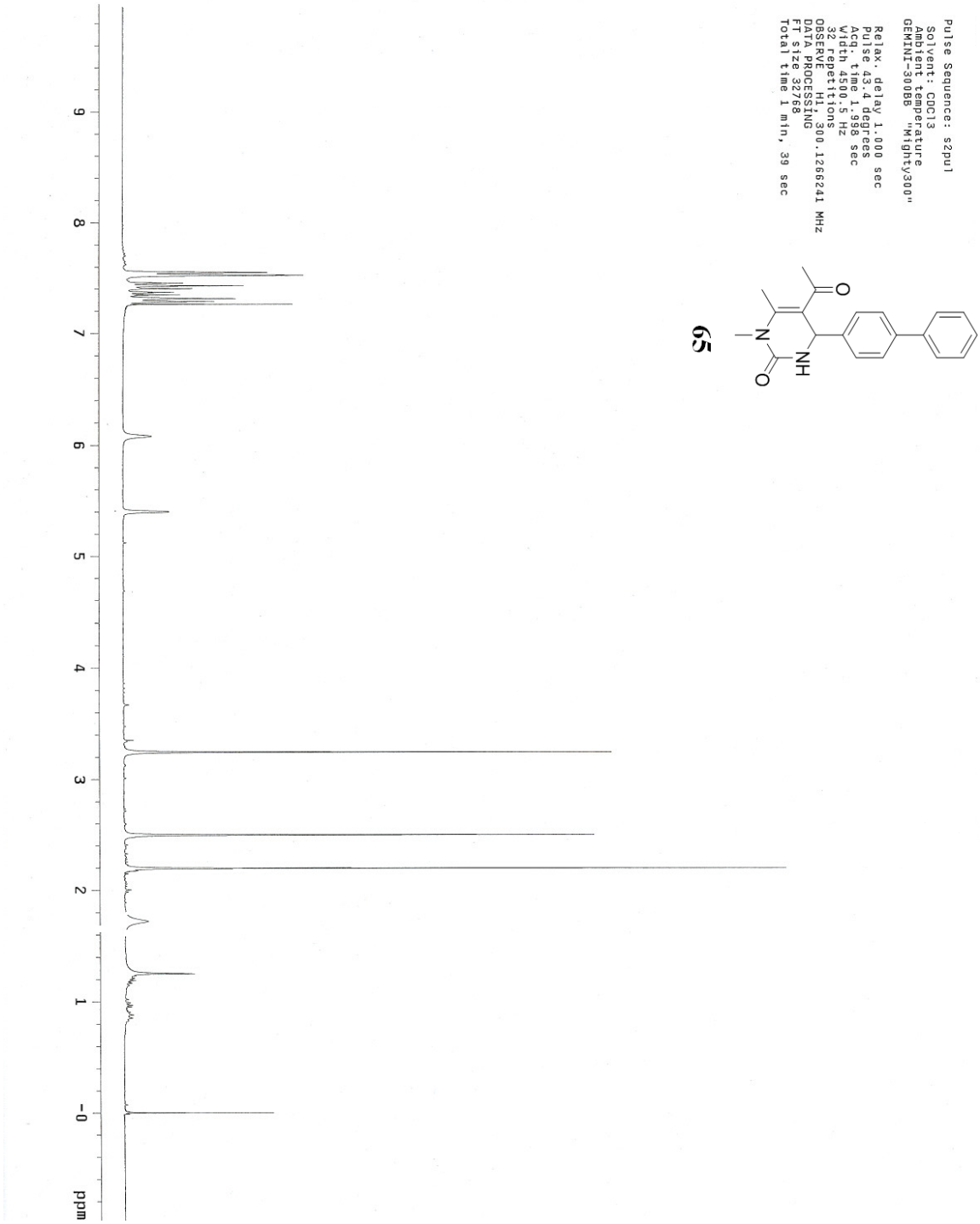


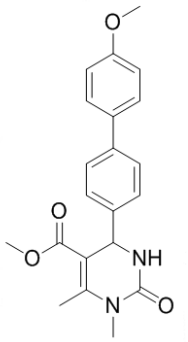




MS Spectrum




Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1 300.1266241 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec
69
O
N
NH
O
9
8
7
6
5
4
3
2
1
-0
ppm

**Product 66**



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Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-05-04\001-0101.D
Sample Name : A2B3C5D1
======================================================================
Acq. Operator   : B                              Seq. Line :   1
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 5/4/2011 12:33:55 PM                Inj :   1
                                                 Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
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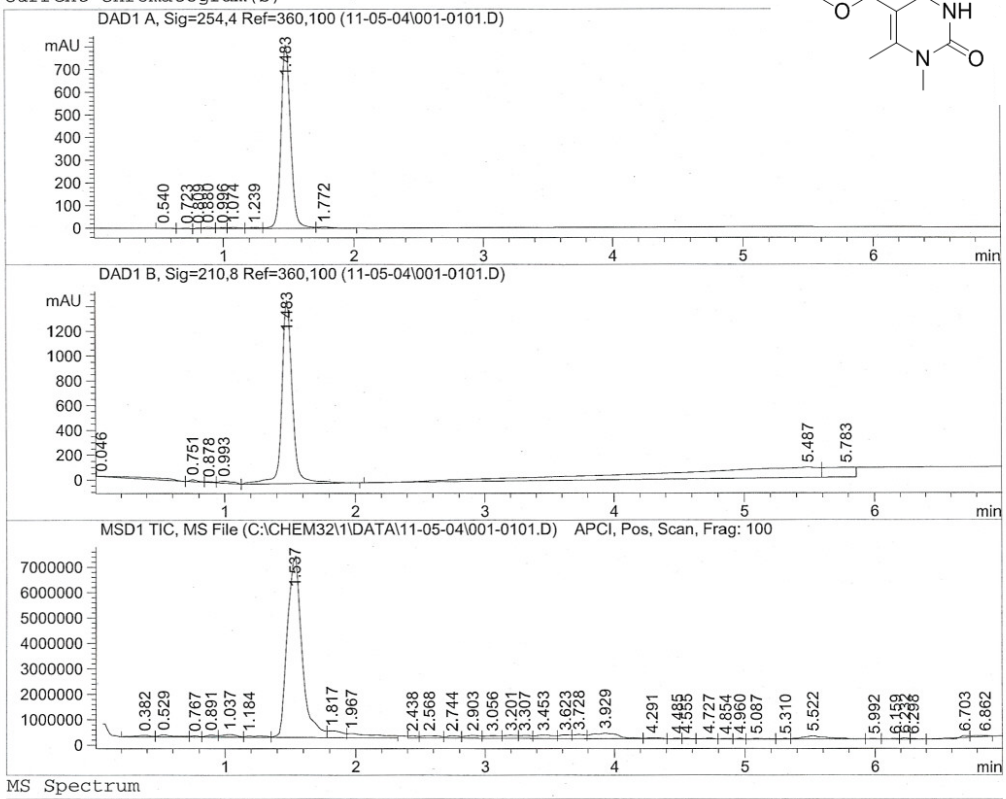
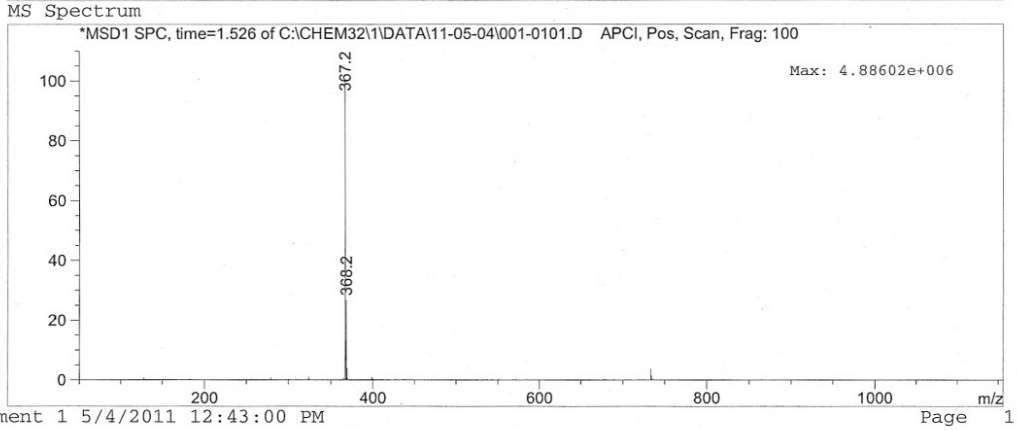
Current Chromatogram(s)



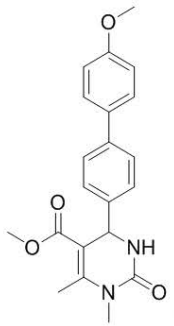

MS Spectrum



STANDARD 1H OBSERVE

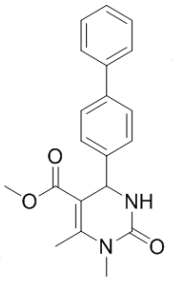
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.1266188 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec




**66**

**Product 67**



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Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-04-12\031-0101.D
Sample Name : A2B3C5D2
======================================================================
Acq. Operator   : B                          Seq. Line :   1
Acq. Instrument : Instrument 1               Location : Vial 31
Injection Date  : 4/12/2011 6:21:36 PM           Inj :   1
                                           Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 3/10/2011 9:35:54 PM by Z
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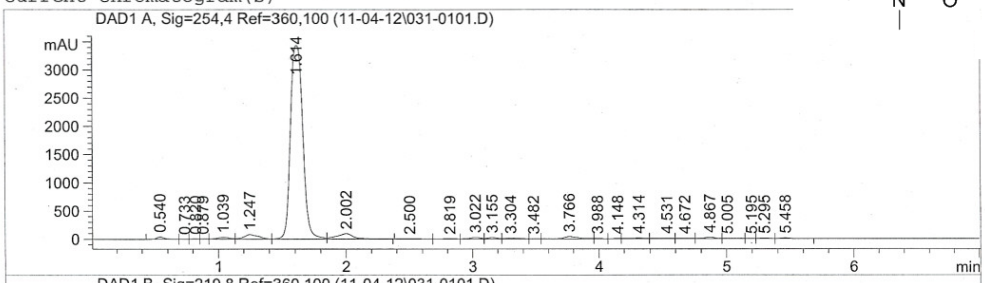
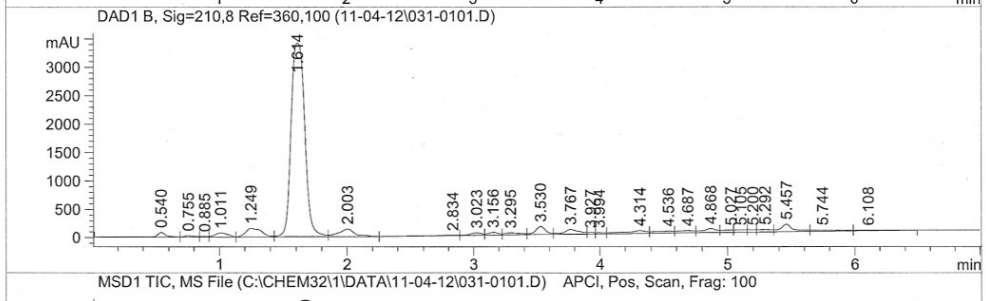
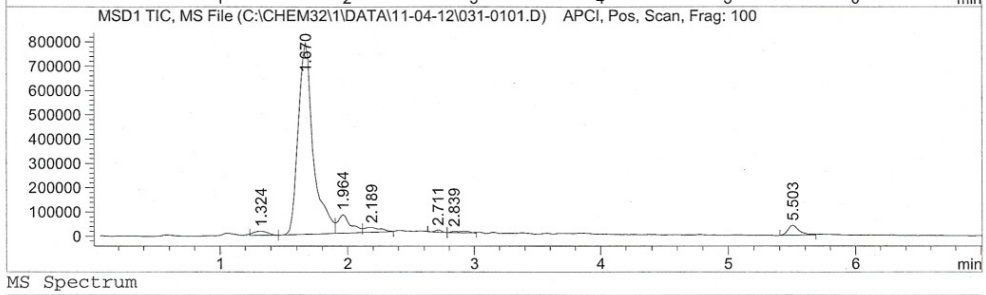
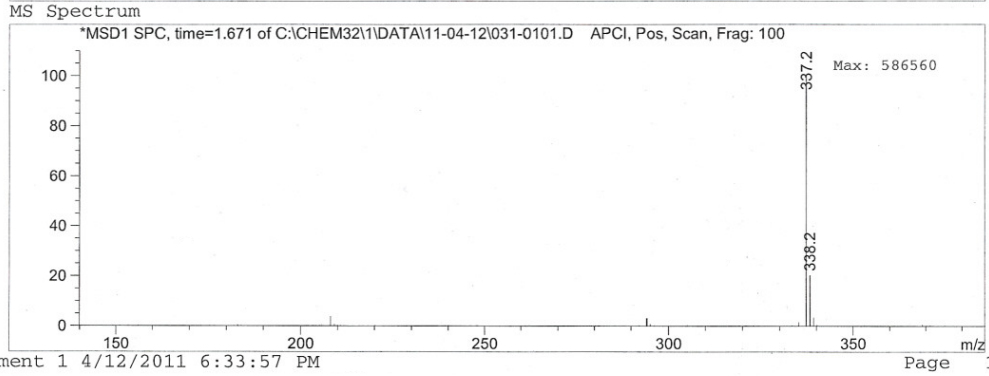
Current Chromatogram(s)




MS Spectrum

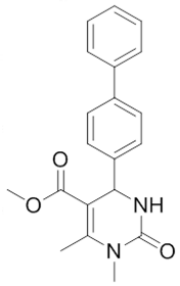



Instrument 1 4/12/2011 6:33:57 PM Page 1 of 1

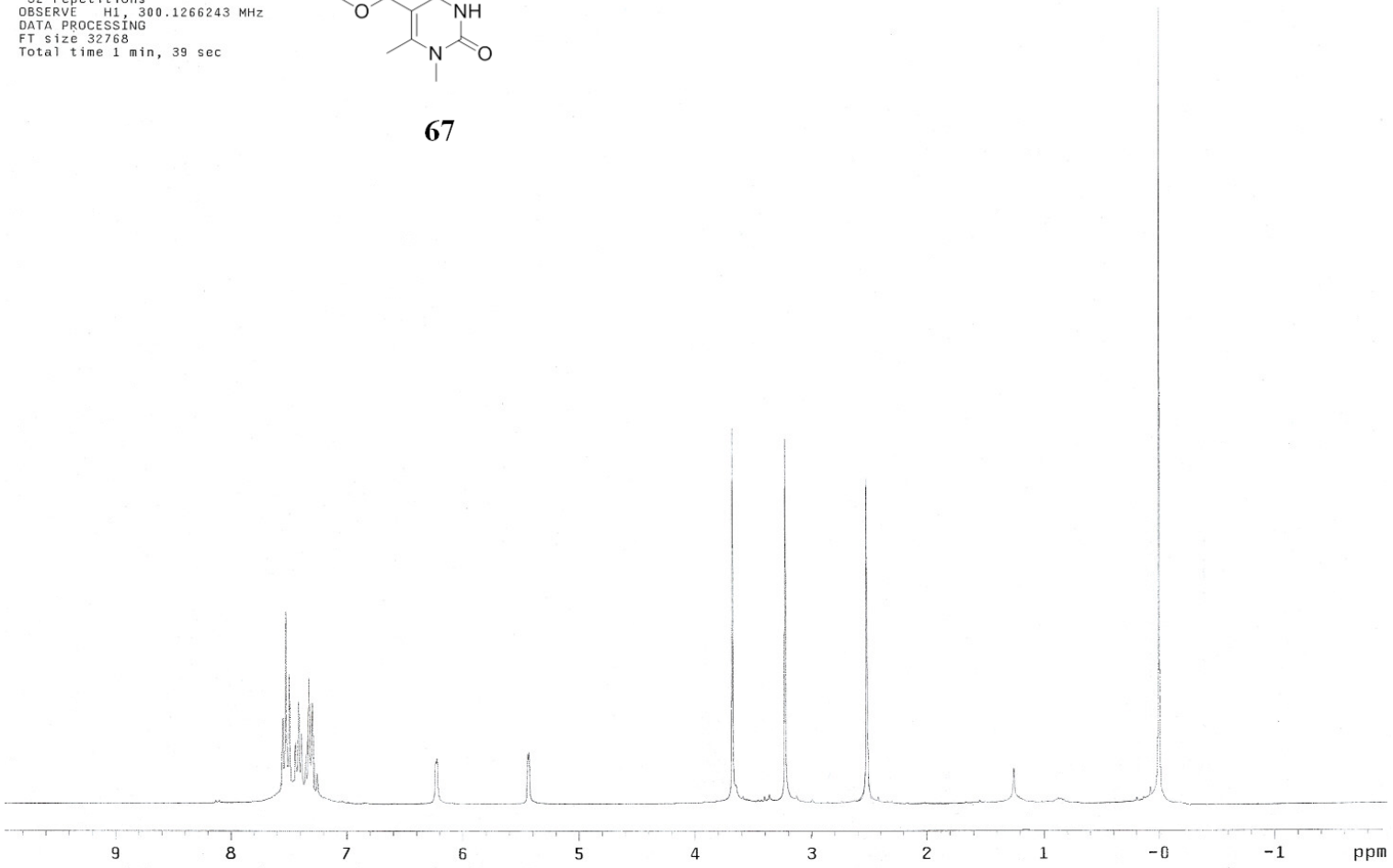
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266243 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



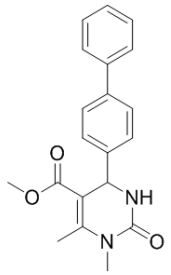

**67**



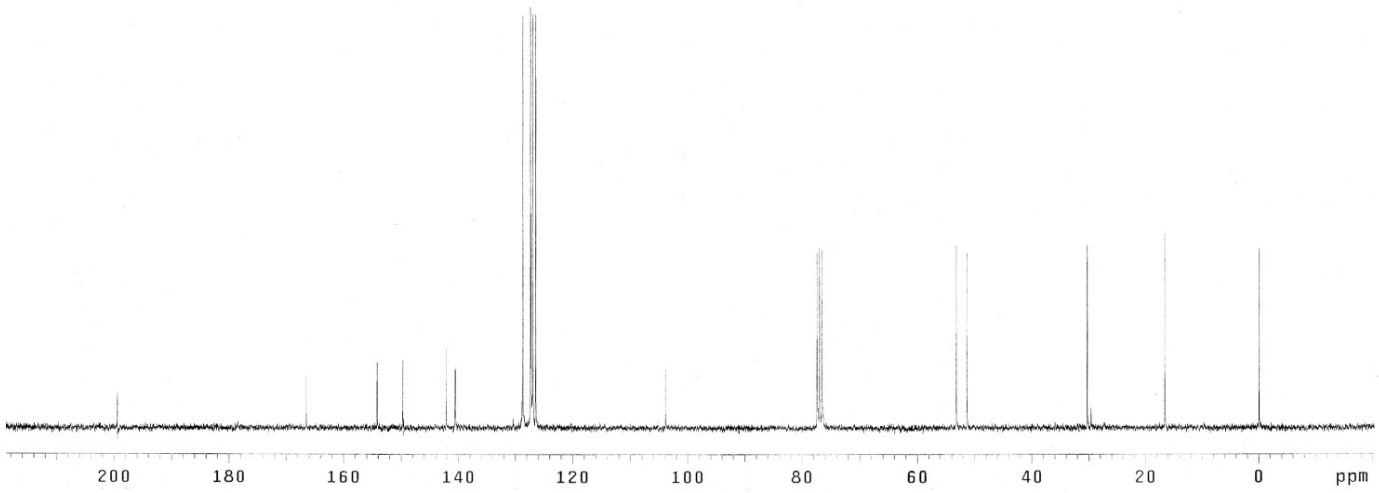
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 2.000 sec
Pulse 67.8 degrees
Acq. time 1.815 sec
Width 20000.0 Hz
1024 repetitions
OBSERVE C13, 75.4669049 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 0 min, 0 sec




**67**

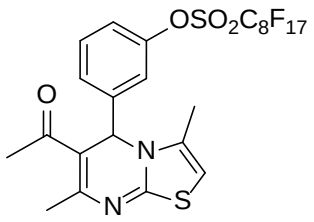


APPENDIX E

SUPPORTING INFORMATION AND PRODUCT CHARACTERIZATION FOR

CHAPTER 3.5

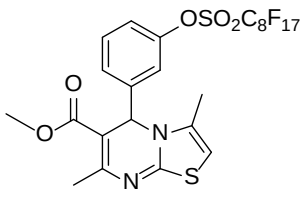
**1-(5-(3-fluorophenyl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (74):**




LC-MS (APCI+) *m/z* 783 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.85 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 3.0 Hz, 1H), 7.43-7.32 (m, 2H), 7.28-7.17 (m, 2H), 6.44 (s, 1H), 6.06 (s, 1H), 2.42 (s, 6H), 2.08 (s, 3H).

**Methyl-5-(3-perfluorooctanesulfonyl)-3,7-dimethyl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (75):**

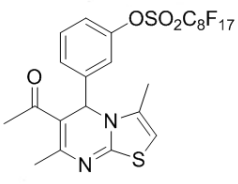



LC-MS (APCI+) *m/z* 798 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.85 (d, *J* = 7.5Hz, 1H), 7.74 (d, *J* = 2.7 Hz, 1H), 7.43-7.32 (m, 2H), 7.27-7.18 (m, 2H), 6.22 (s, 1H), 6.06 (s, 1H), 3.75 (s, 3H), 2.40 (s, 3H), 2.07 (s, 3H).

$^{13}$C NMR (75.5MHz, $CDCl_3$), δ 169.7, 165.5, 153.8, 152.7, 149.6, 143.2, 135.0, 131.2, 128.5, 126.3, 121.6, 120.5, 119.5, 118.9, 118.3, 117.7, 117.0, 116.2, 114.4, 113.7, 57.2, 51.1, 23.1, 13.8.

**Product 74**

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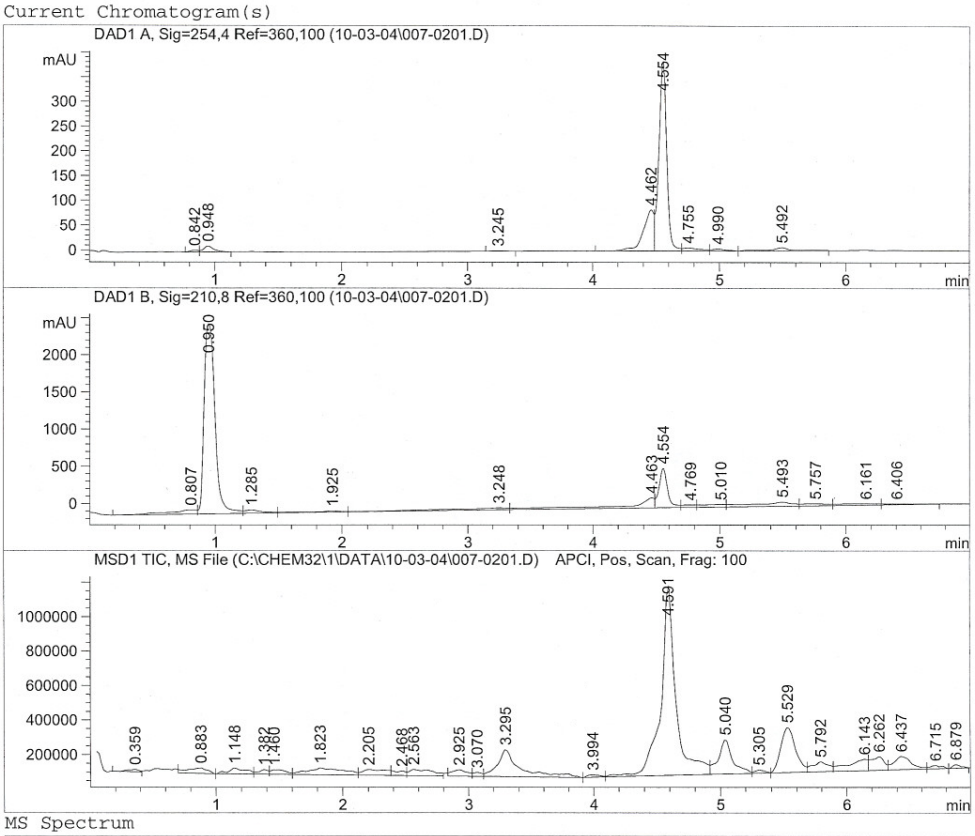
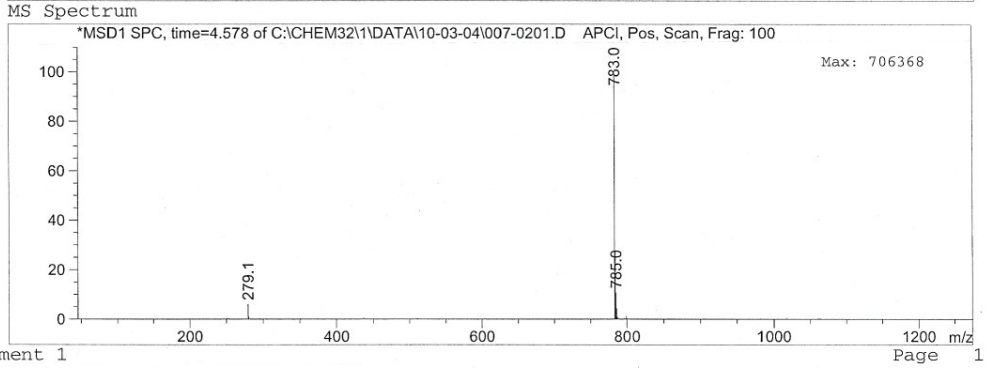
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-03-04
Sample Name : A5B1C6
======================================================================
Acq. Operator   : B                          Seq. Line :   2
     Instrument : Instrument 1                Location : Vial 7
Injection Date  : 3/4/2010 7:45:54 PM             Inj :   1
                                            Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 1/19/2010 4:54:55 PM by  J
```

Current Chromatogram(s)



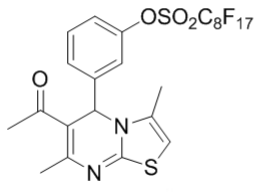

MS Spectrum



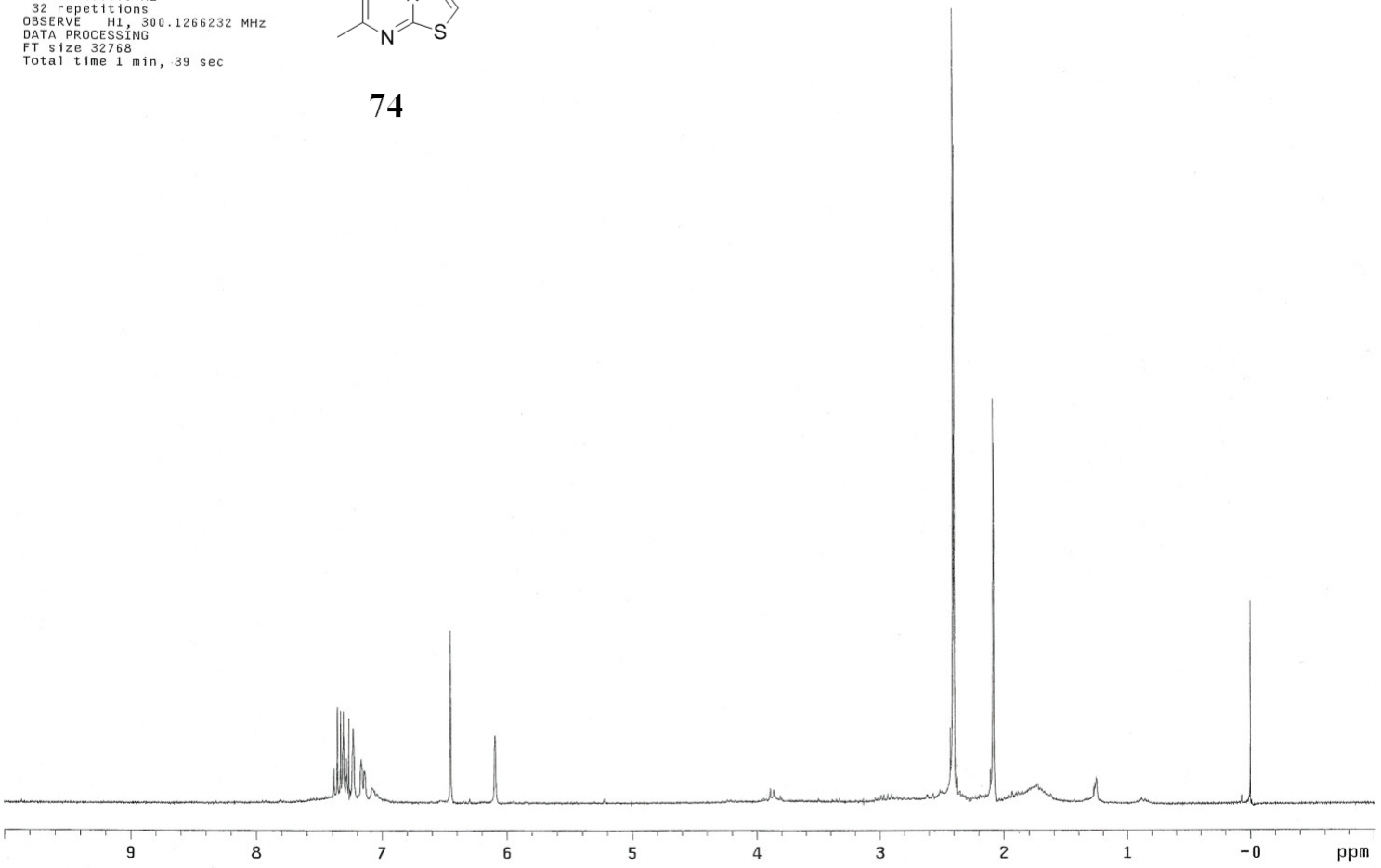
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266232 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

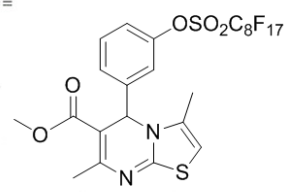



**74**



Print of all graphic windows
Data File : C:\CHEM32\1\DATA\11-05-25
Sample Name : A5B1C5 Cycl

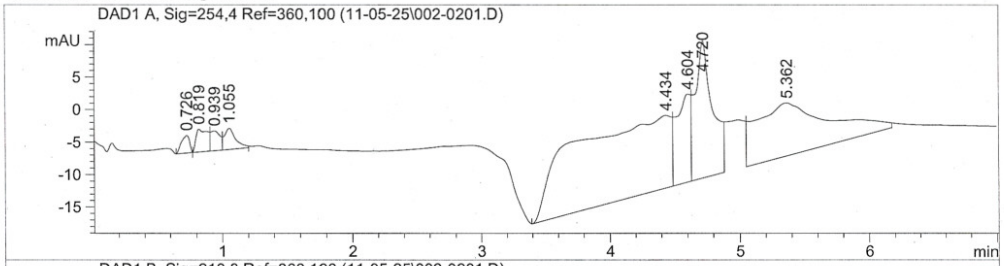
**Product 75**

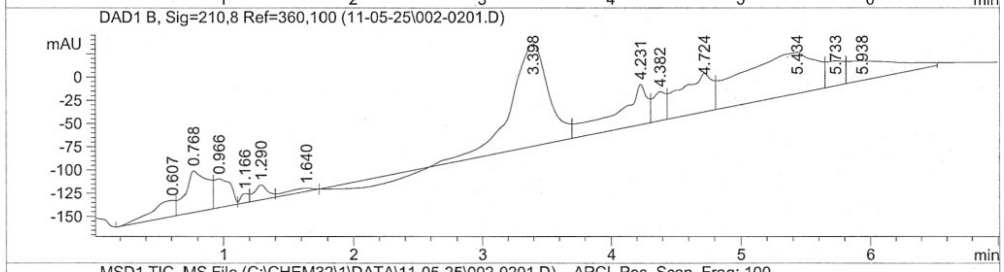


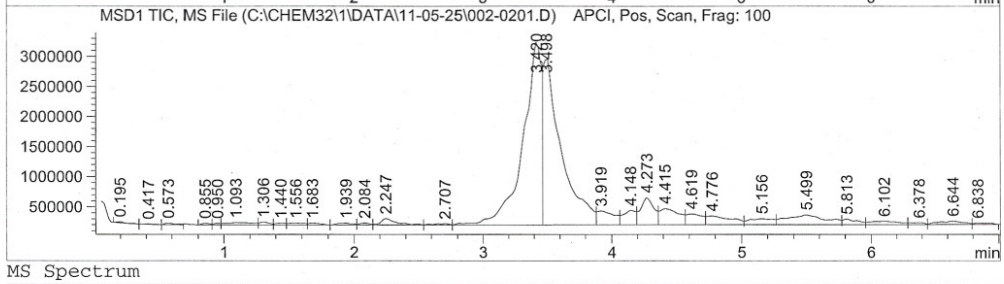

| | | | |
|---|---|---|---|
| Acq. Operator | : T | Seq. Line | : 2 |
| Acq. Instrument | : Instrument 1 | Location | : Vial 2 |
| Injection Date | : 5/25/2011 12:15:17 PM | Inj | : 1 |
| | | Inj Volume | : 4 µl |

Method : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed : 4/27/2011 11:04:42 AM by J

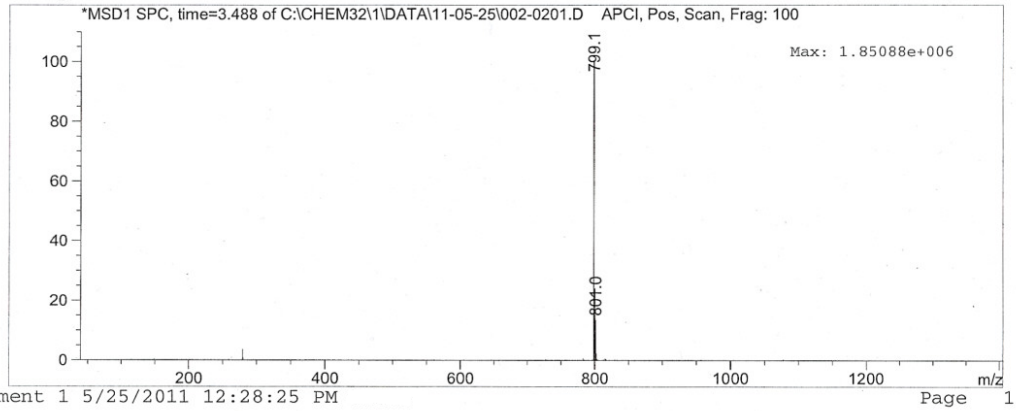
Current Chromatogram(s)



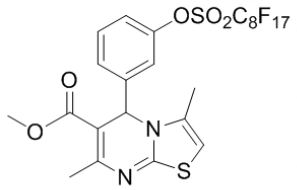

MS Spectrum



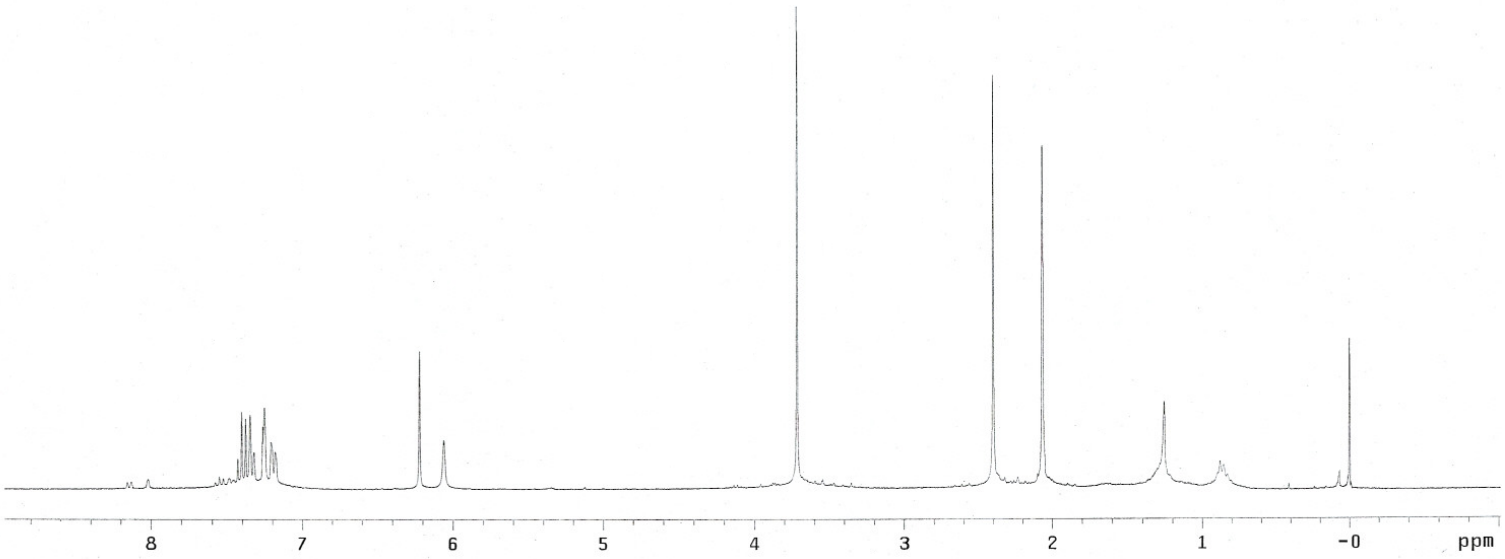
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266235 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



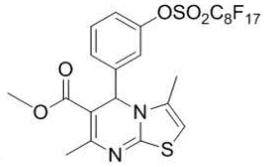

**75**



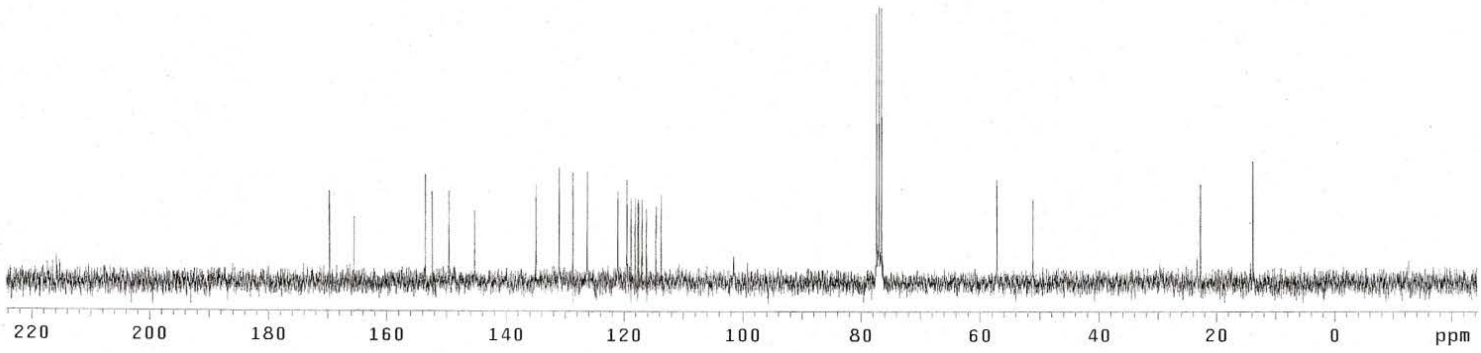
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Pulse 67.8 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
1024 repetitions
OBSERVE C13, 75.4669007 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 36 min, 3 sec




**75**

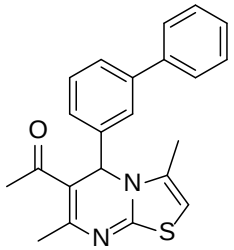


APPENDIX F

SUPPORTING INFORMATION AND PRODUCT CHARACTERIZATION FOR

CHAPTER 3.6

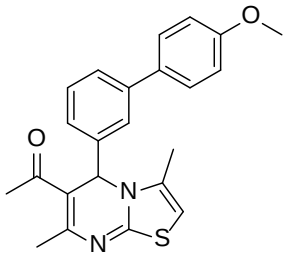
**1-(5-([1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (76):**




LC-MS (APCI+) *m/z* 361 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.48 (s, 1H), 7.41-34 (m, 4H), 7.32-7.27 (m, 4H), 6.43 (s, 1H), 6.17 (s, 1H), 2.40 (s, 6H), 2.16 (s, 3H).

**Methyl-5-(4'-methoxy-[1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (77):**

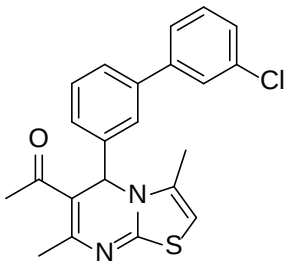



LC-MS (APCI+) *m/z* 391 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.49-7.41 (m, 3H), 7.32-6.09 (m, 3H), 6.96 (d, *J* = 10.0 Hz, 2H), 6.68 (s, 1H), 6.16 (s, 1H), 3.84 (s, 3H), 2.40 (s, 6H), 2.12 (s, 3H).

$^{13}$C NMR (75.474 MHz, $CDCl_3$), δ 169.8, 166.5, 153.8, 152.7, 147.8, 141.1 136.4, 132.9, 129.2, 128.1, 126.4 124.6, 114.2, 57.2, 55.3, 51.3, 24.5, 13.9.

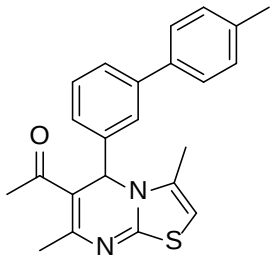
**1-(5-(3'-chloro-[1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (78):**




LC-MS (APCI+) *m/z* 395 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.50 (s, 1H), 7.46 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.38-7.31 (m, 5H), 6.49 (s, 1H), 6.16 (s, 1H), 2.45 (s, 3H), 2.18 (s, 3H).

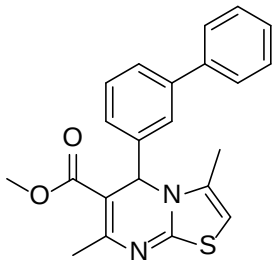
**1-(3,7-dimethyl-5-(4'-methyl-[1,1'-biphenyl]-3-yl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (79):**



LC-MS (APCI+) *m/z* 375 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.45 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.23 (t, *J* = 14.5 Hz, 1H), 7.23-7.14 (m, 4H), 6.41(s, 1H), 5.89 (s, 1H), 2.32 (s, 6H), 2.03 (s, 3H).

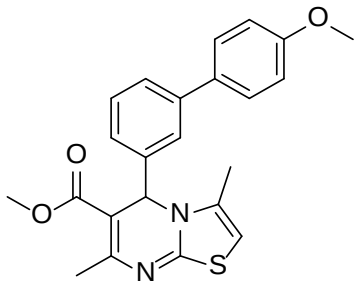
**Methyl 5-([1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (80):**



LC-MS (APCI+) *m/z* 377$[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.49 (t, *J* = 13.5 Hz, 2H), 7.49 (t, *J* = 13.5 Hz, 1H), 7.38-7.28 (m, 5H), 7.24 (s, 1H), 6.42 (s, 1H), 6.16 (s, 1H), 3.86 (s, 3H), 2.41 (s, 3H), 2.05 (s, 3H).

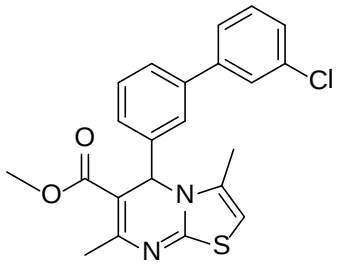
**Methyl 5-(4'-methoxy-[1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (81):**




LC-MS (APCI+) *m/z* 377$[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.46 (s, 1H), 7.34 (t, *J* = 15 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 4H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 6.22 (s, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 2.46 (s, 3H), 2.12 (s, 3H).

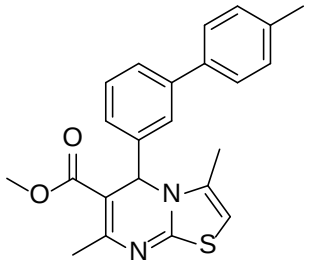
**Methyl 5-(3'-chloro-[1,1'-biphenyl]-3-yl)-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (82):**




LC-MS (APCI+) *m/z* 411 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.59 (s, 1H), 7.54(s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.38-7.31 (m, 5H) 6.28 (s, 1H), 6.16 (s, 1H), 3.73 (s, 3H), 2.39 (s, 3H), 2.11 (s, 3H).

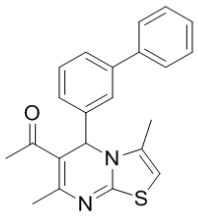
**Methyl 3,7-dimethyl-5-(4'-methyl-[1,1'-biphenyl]-3-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (83):**




LC-MS (APCI+) *m/z* 391 $[M+1]^+$.

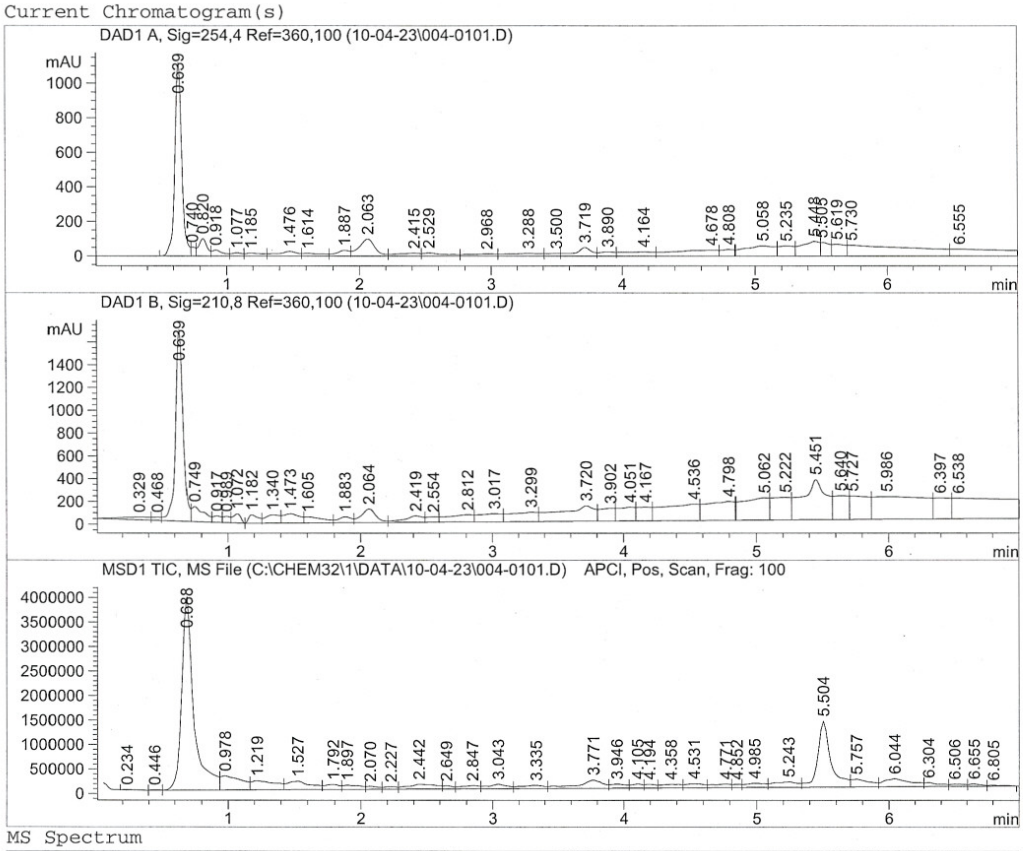
$^1$H NMR (300 MHz, $CDCl_3$), δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (s, 1H), 7.36 (t, *J* = 12.0 Hz, 1H), 7.29-7.17 (m, 4H), 6.56 (s, 1H), 6.17 (s, 1H), 3.76 (s, 3H), 2.38 (s, 3H), 1.96 (s, 3H).

**Product 76**

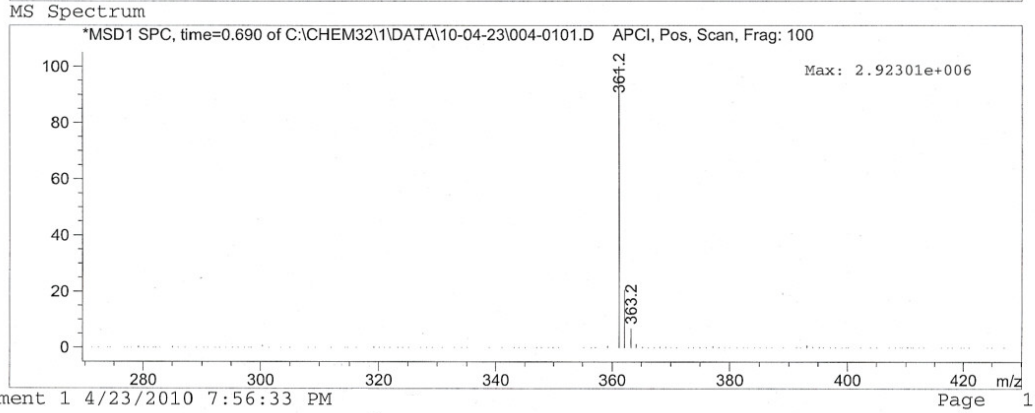


```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-04-23\004-0101.D
Sample Name : A5B1C6+D2 Display
======================================================================
Acq. Operator   : E                          Seq. Line :   1
A    Instrument : Instrument 1                Location : Vial 4
Injection Date  : 4/23/2010 7:46:13 PM             Inj :   1
                                            Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/14/2010 4:33:44 PM by J
```

Current Chromatogram(s)



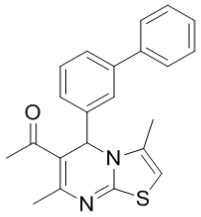

MS Spectrum



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

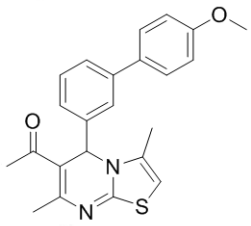
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266235 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



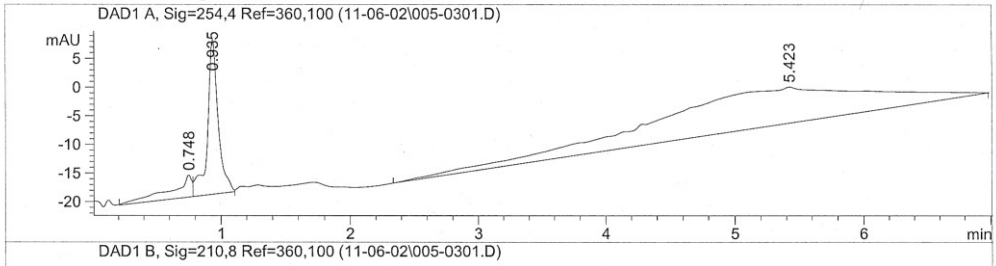

**76**

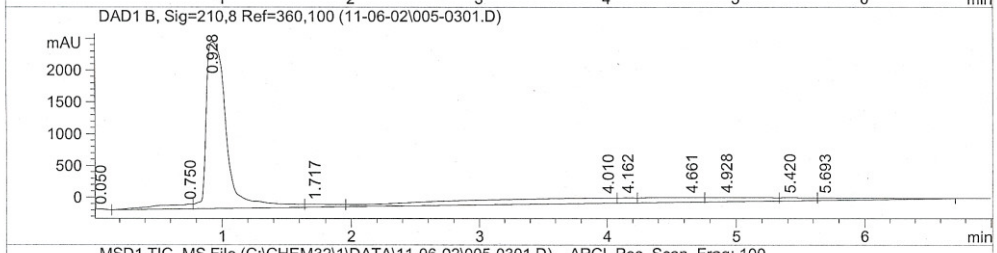
**Product 77**

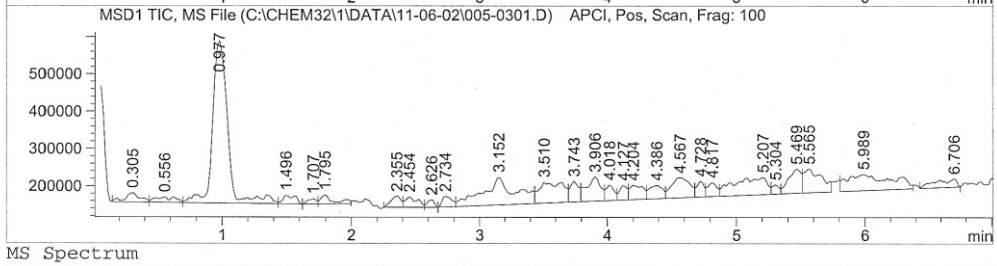
```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-06-02\005-0301.D
Sample Name : A5B1C5D1 CYCLOA W1
======================================================================
Acq. Operator   : B                                 Seq. Line :   3
Acq. Instrument : Instrument 1                       Location : Vial 5
Injection Date  : 6/2/2011 6:44:48 PM                    Inj :   1
                                                   Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
Sample Info     :
```



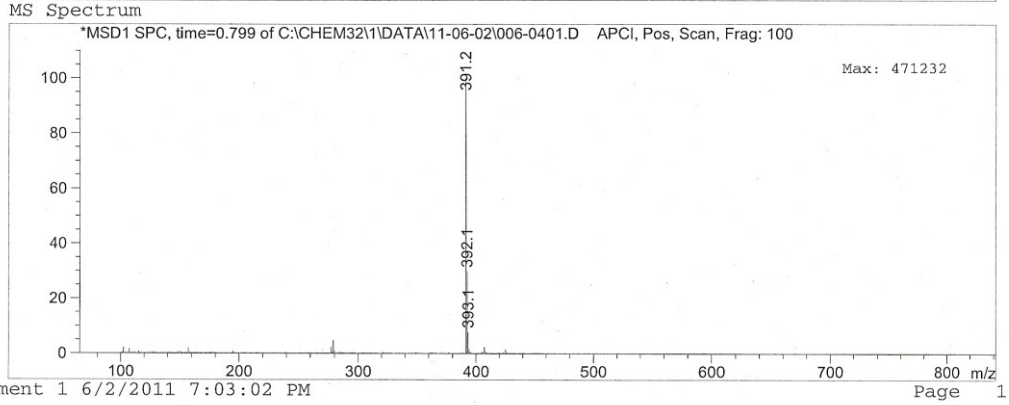

Current Chromatogram(s)



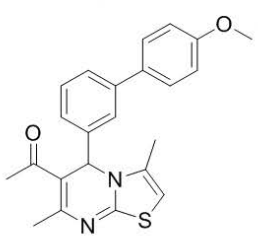

MS Spectrum



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 24.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266235 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

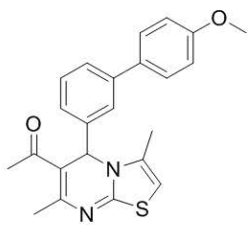



77

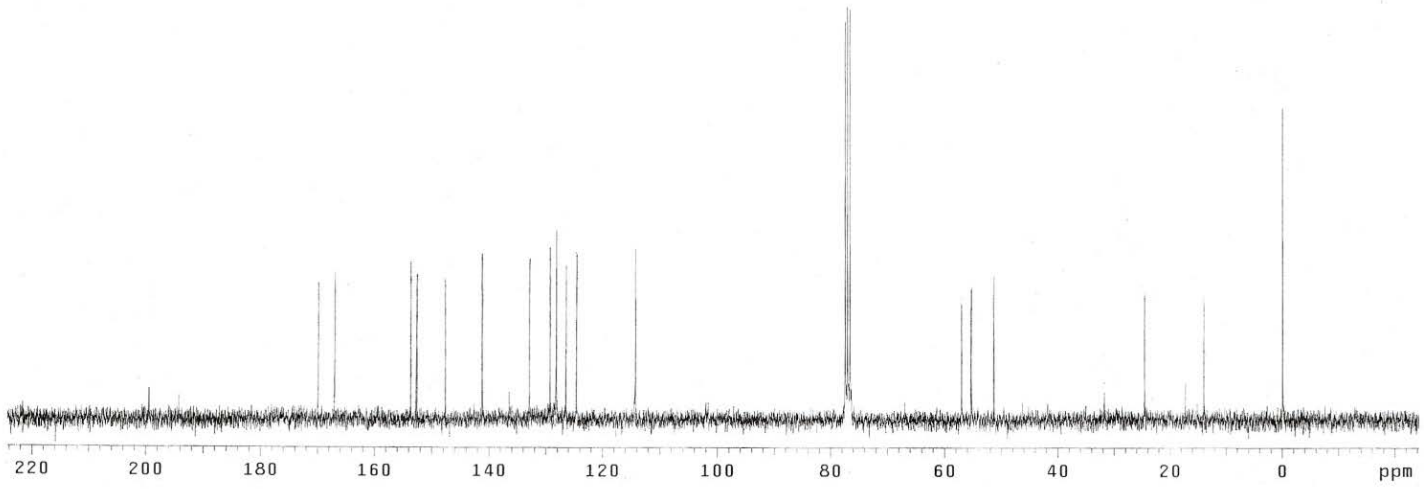
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

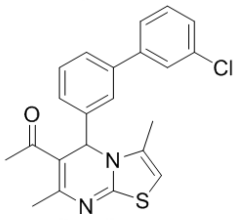
Pulse 75.9 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
2048 repetitions
OBSERVE C13, 75.4669015 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 12 min, 7 sec




77

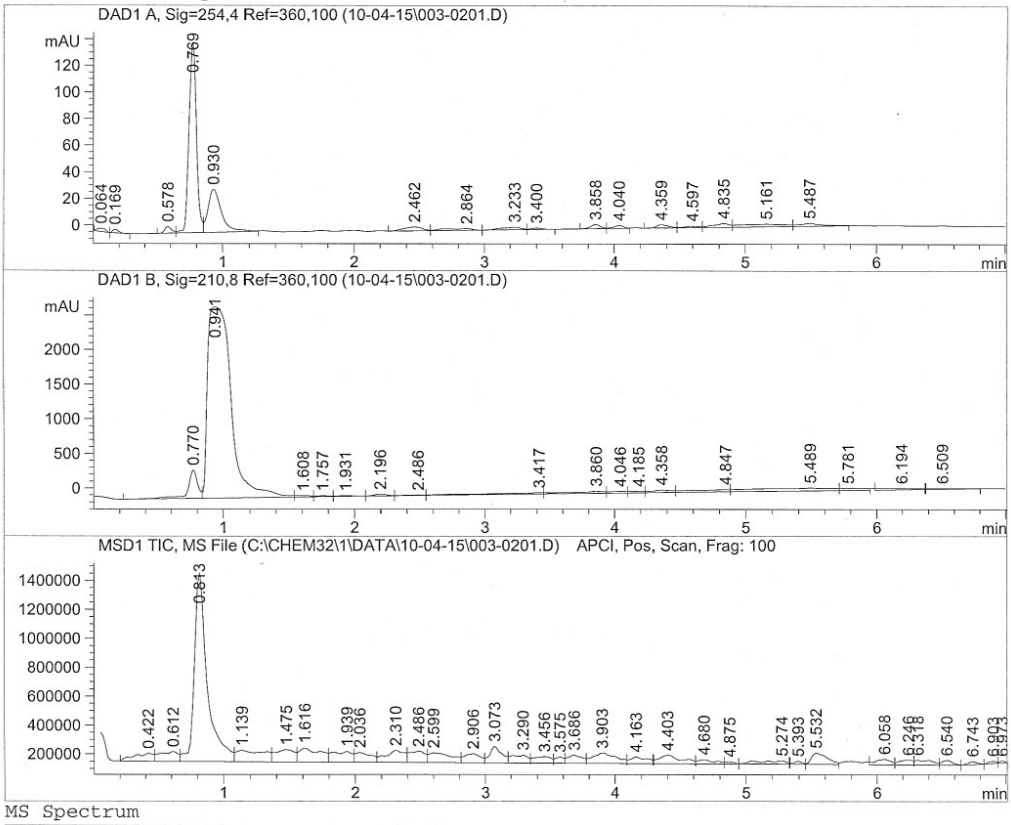


**Product 78**

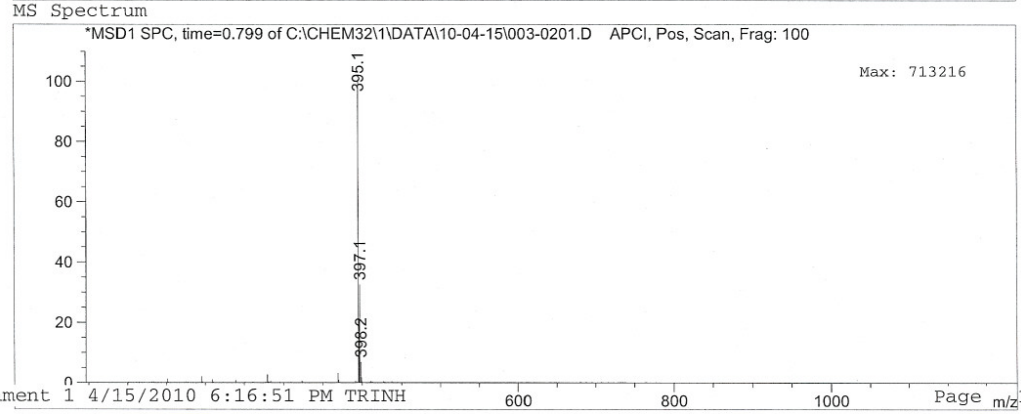


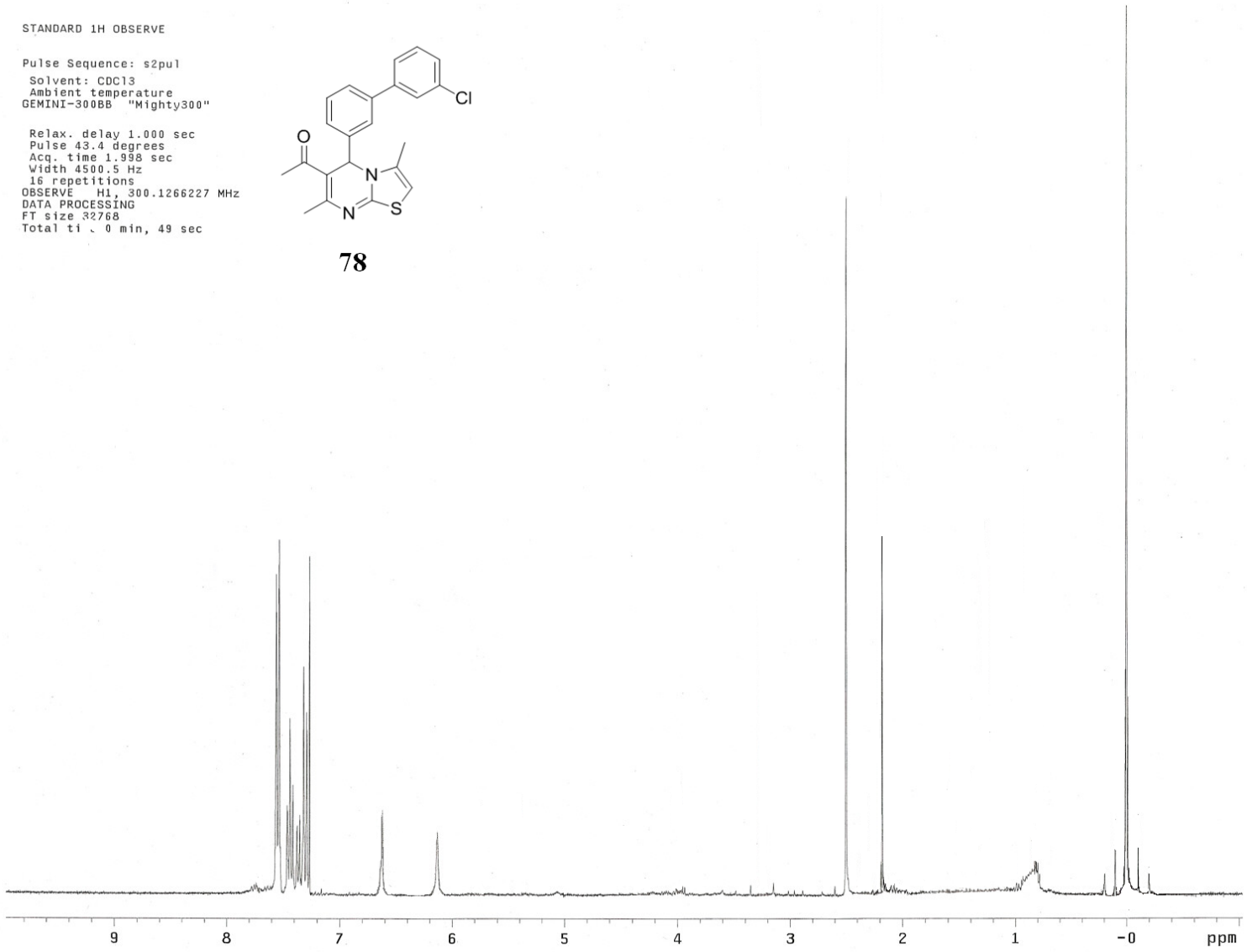

```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-04-15\003-0201.D
Sample Name : A5B1C6+D3 Cycloa Suz
======================================================================
Acq. Operator   : E                          Seq. Line :   2
Instrument      : Instrument 1                Location : Vial 3
Injection Date  : 4/15/2010 5:59:24 PM           Inj :   1
                                           Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/14/2010 4:33:44 PM by J
```

Current Chromatogram(s)




MS Spectrum

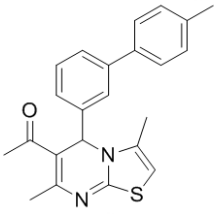



STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.1266227 MHz
DATA PROCESSING
FT size 32768
Total ti . 0 min, 49 sec
O
N
N
S
Cl
9
8
7
6
5
4
3
2
1
-0
ppm

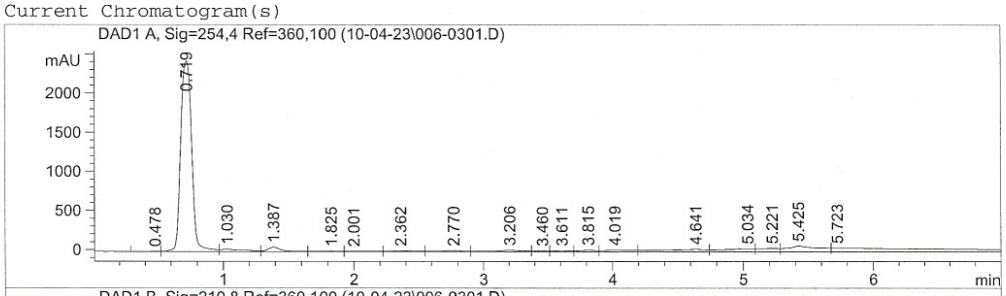
**78**

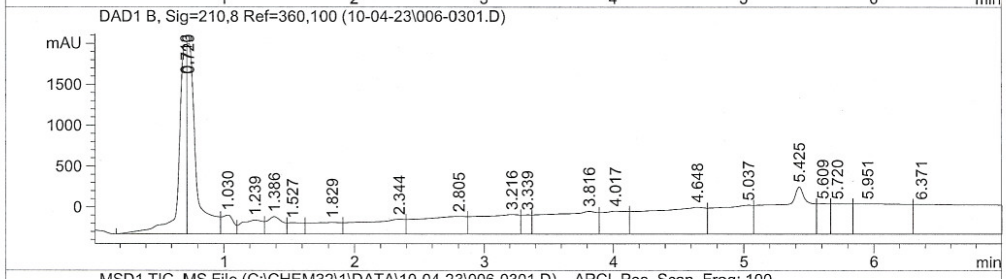
**Product 79**

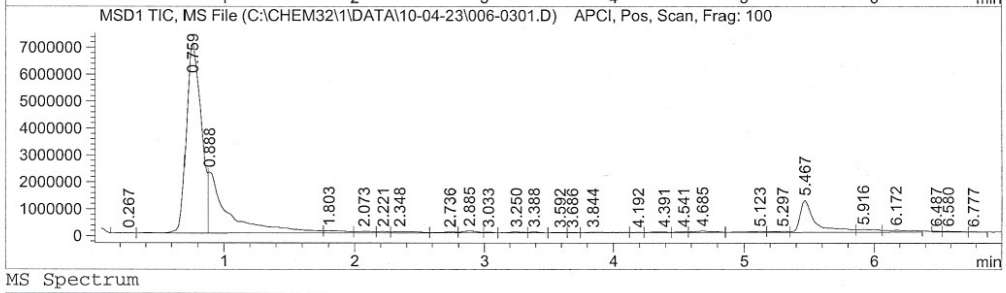
```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-04-23\006-0301.D
Sample Name : A5B1C6+D4 Display
======================================================================
Acq. Operator   : B                          Seq. Line :   3
     Instrument : Instrument 1                Location : Vial 6
Injection Date  : 4/23/2010 8:03:07 PM            Inj :   1
                                             Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/14/2010 4:33:44 PM by J
```



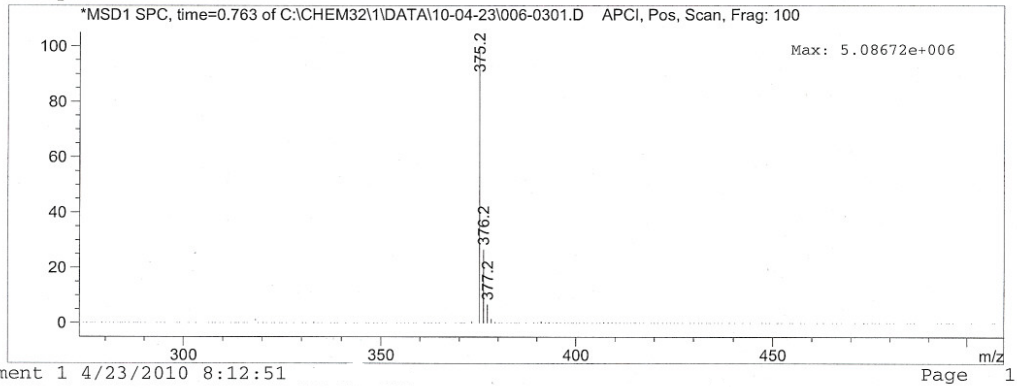

Current Chromatogram(s)



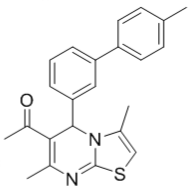

MS Spectrum



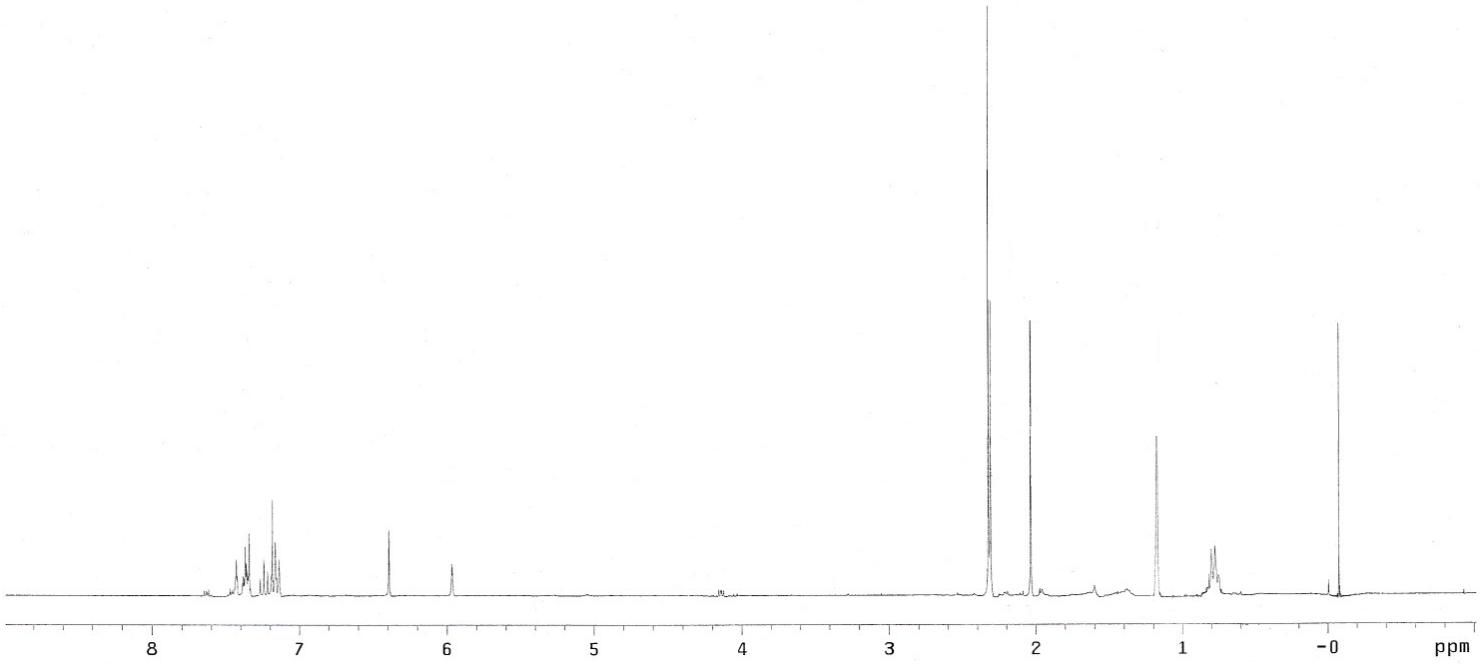
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266478 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

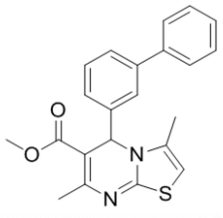



**79**

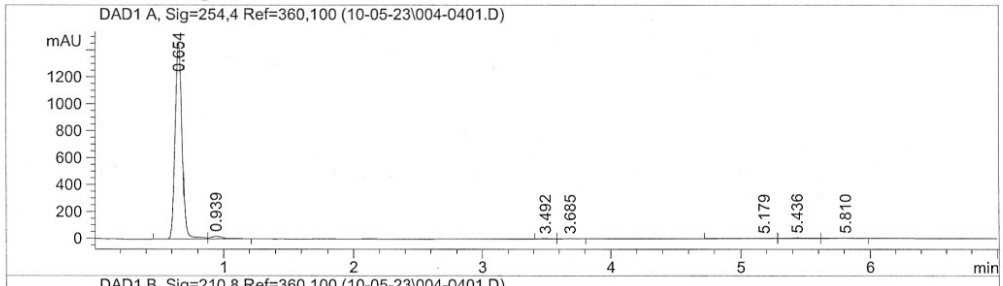


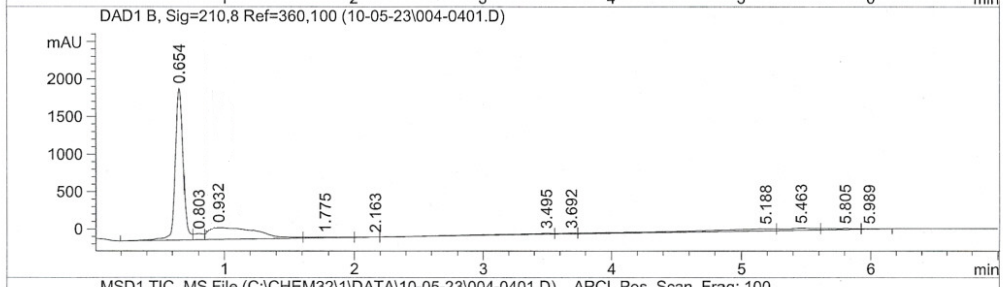
**Product 80**

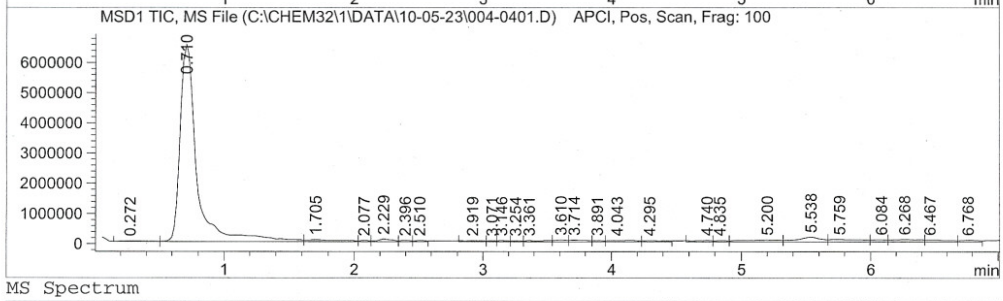
```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-0 -23\004-0401.D
Sample Name : Cycloa A6B1C5+D2
======================================================================
Acq. Operator   : B                              Seq. Line :   4
A    Instrument : Instrument 1                    Location : Vial 4
I.   ection Date : 5/23/2010 6:11:59 PM              Inj :   1
                                                 Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/14/2010 4:33:44 PM by J
```



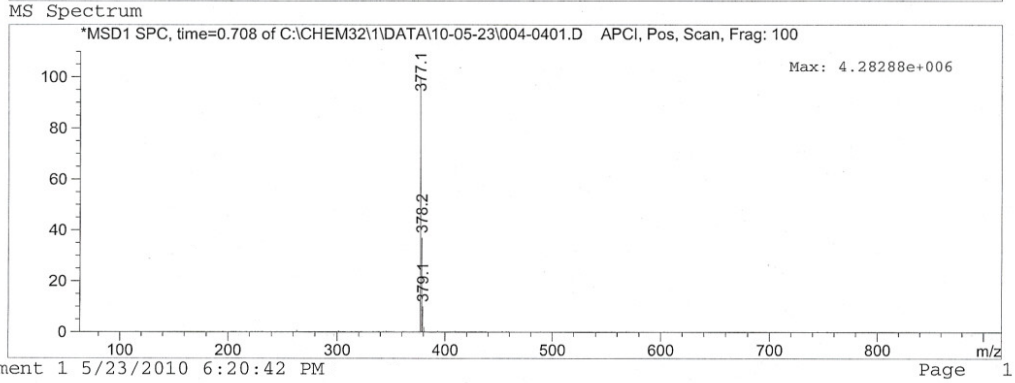
Current Chromatogram(s)



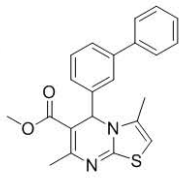

MS Spectrum



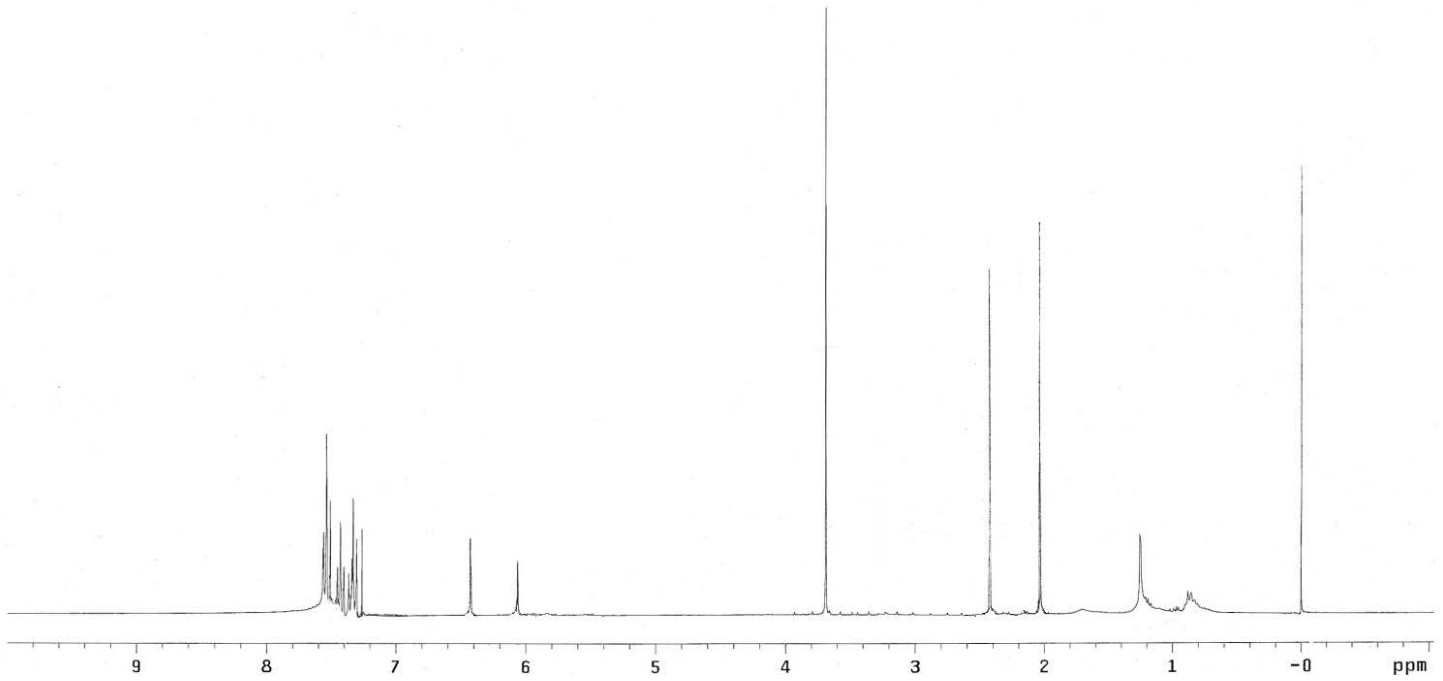
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

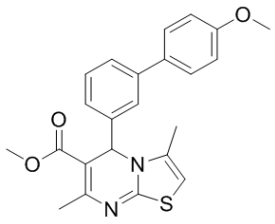
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266246 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec




**80**

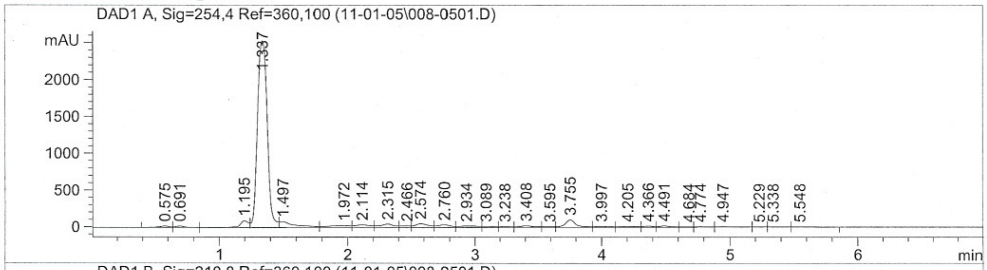


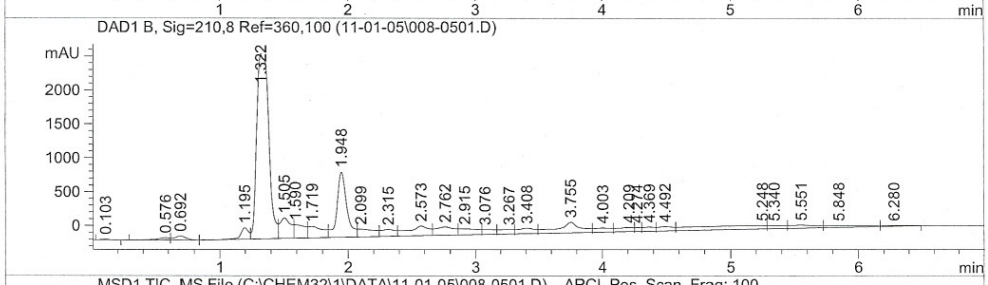
**Product 81**

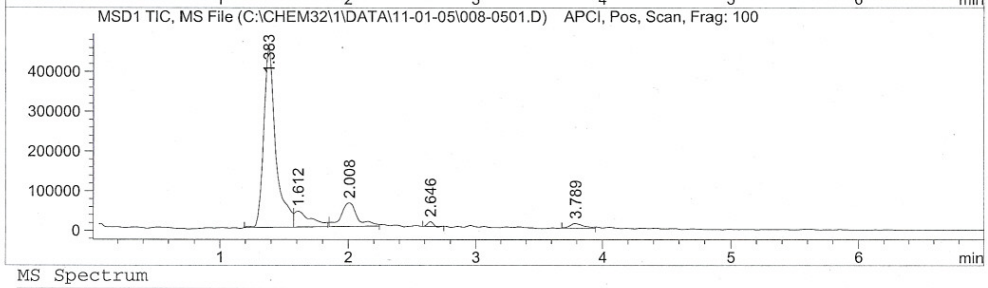


```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-01-05\008-0501.D
Sample Name : a6b1c5d1 cycload
======================================================================
Acq. Operator   : H                              Seq. Line :   5
Acq. Instrument : Instrument 1                    Location : Vial 8
Injection Date  : 1/5/2011 5:22:16 PM                Inj :   1
                                                Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 12/23/2010 11:36:52 AM by Z
```

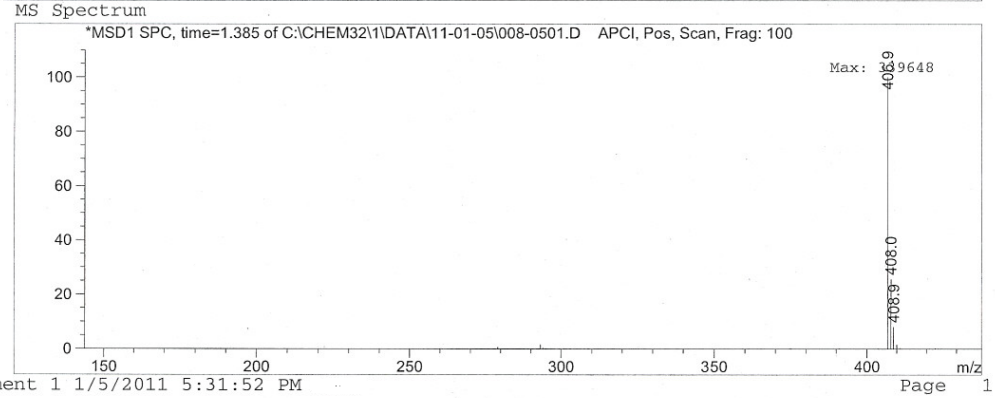
Current Chromatogram(s)



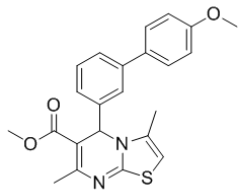

MS Spectrum



STANDARD 1H OBSERVE

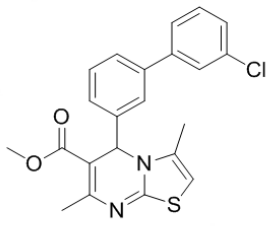
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: CYCLA6B1C6D1
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1266246 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec



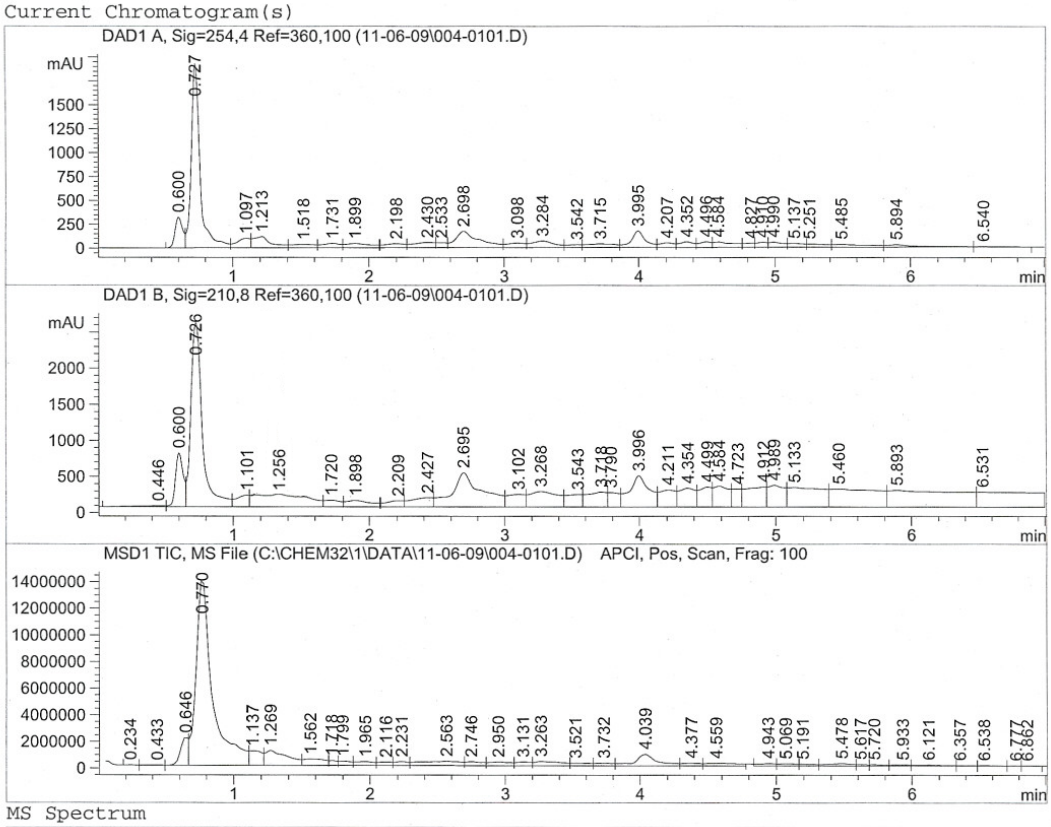

**81**

**Product 82**

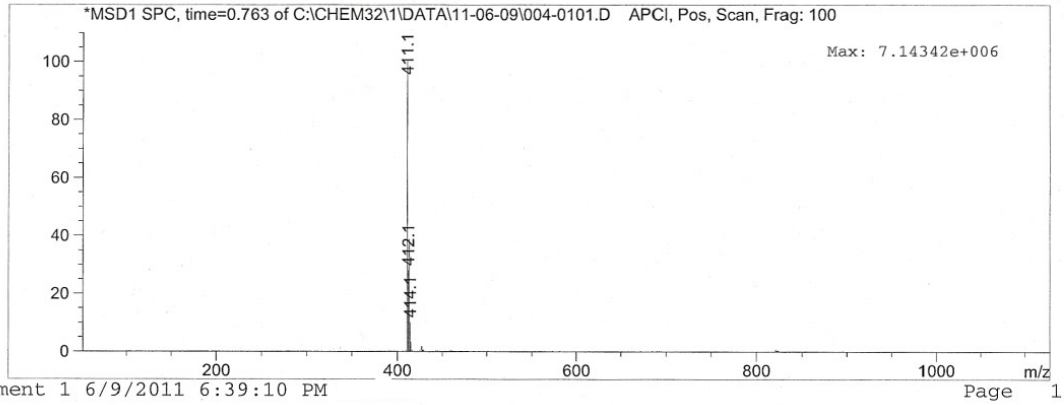


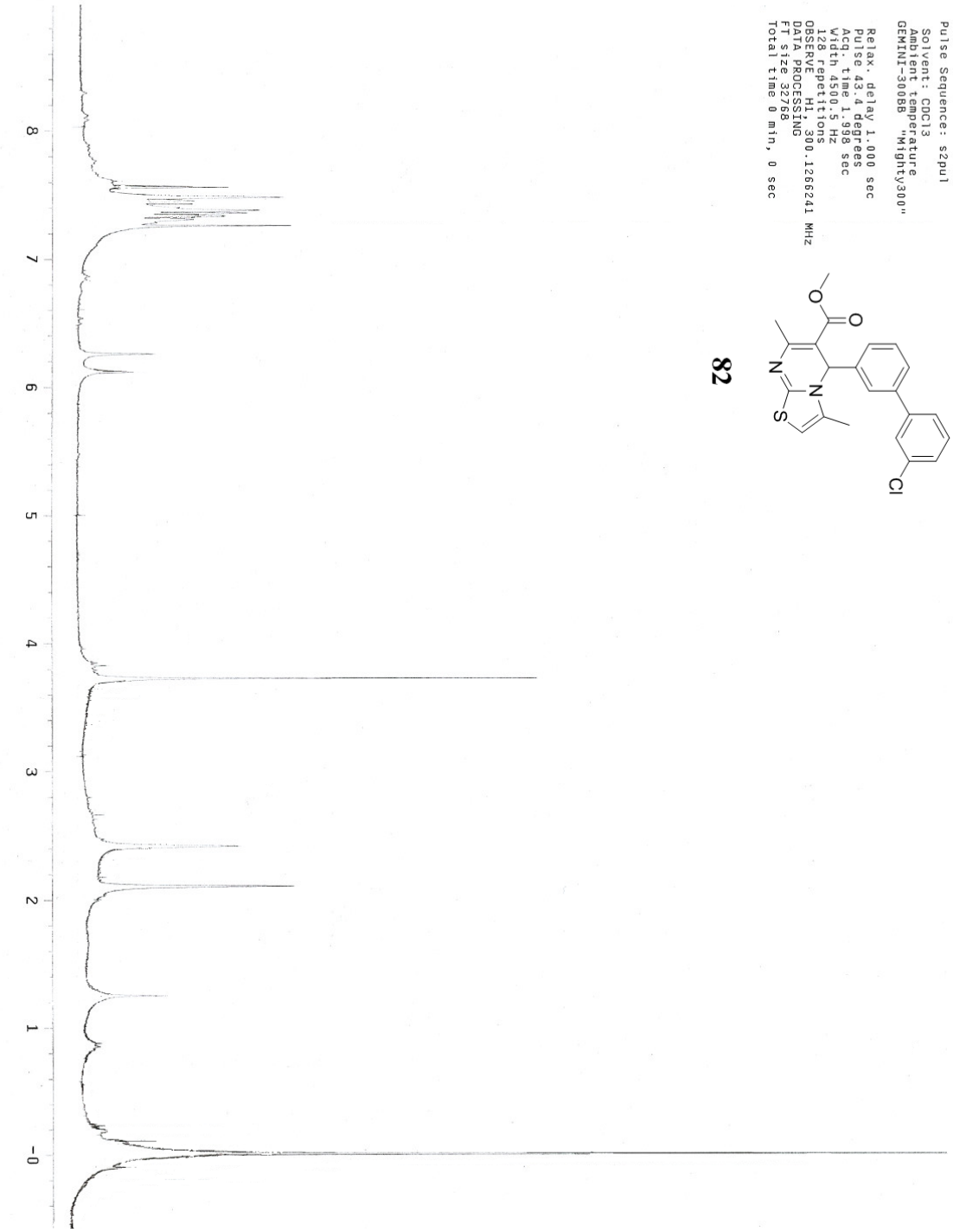

```
==============================================================
Operator    : B                                Seq. Line :   1
Instrument  : Instrument 1                      Location : Vial 4
tion Date   : 6/9/2011 6:30:30 PM                   Inj :   1
                                              Inj Volume : 4 µl
Method      : C:\CHEM32\1\METHODS\GEMETHOD1.M
changed     : 4/27/2011 11:04:42 AM by J
sis Method  : C:\CHEM32\1\METHODS\CINCHONA.M
changed     : 4/22/2011 6:53:22 PM by B
```

Current Chromatogram(s)

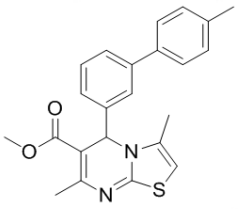



MS Spectrum



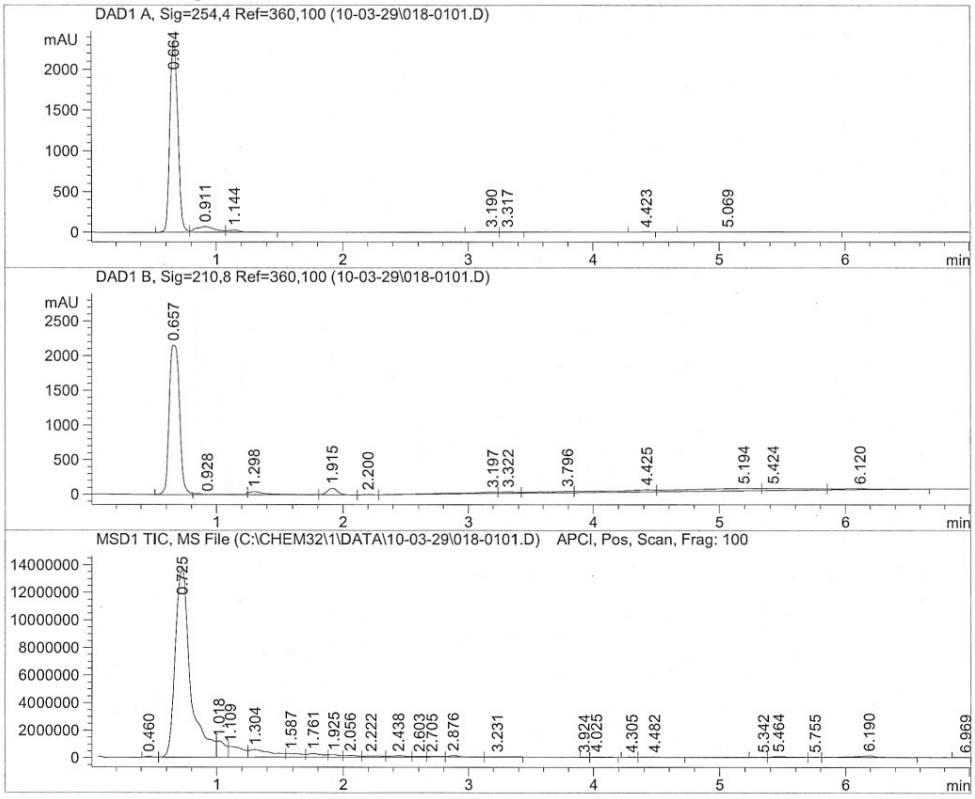

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
128 repetitions
OBSERVE H1, 300.1286241 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
82
O
O
N
N
S
Cl
8
7
6
5
4
3
2
1
0

**Product 83**

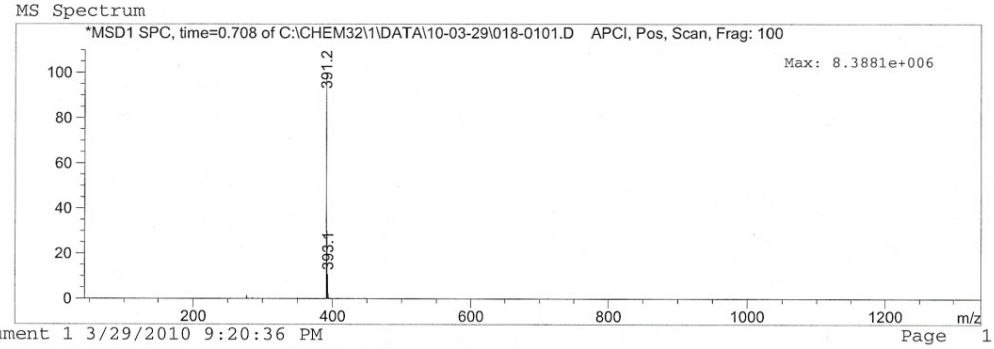


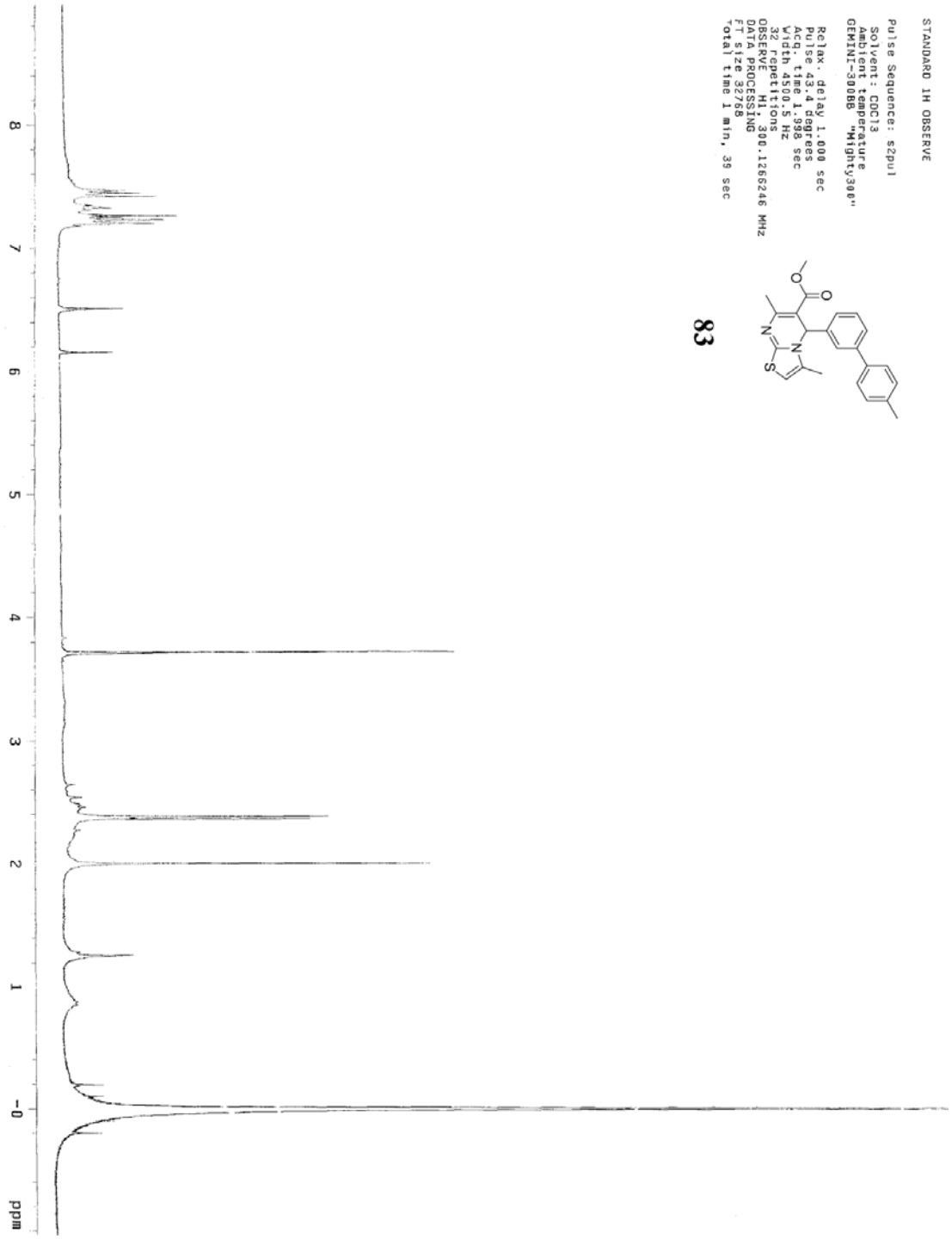
```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\10-03-29\018-0101.D
Sample Name : A5B1C6 Cycloa Suz
======================================================================
Acq. Operator   : B                              Seq. Line :   1
Acquisition Instrument : Instrument 1             Location : Vial 18
Injection Date  : 3/29/2010 9:10:52 PM                Inj :   1
                                                 Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 3/24/2010 5:09:42 PM by H
```

Current Chromatogram(s)




MS Spectrum



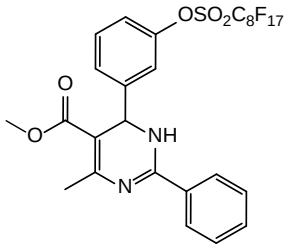

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"
Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.1262246 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec
83
8
7
6
5
4
3
2
1
-0
ppm

APPENDIX G

SUPPORTING INFORMATION AND PRODUCT CHARACTERIZATION FOR

CHAPTER 3.7

**Methyl-4-methyl-2-phenyl-6-(3-perfluorooctanesulfonyl)-1,6-dihydropyrimidine-5-carboxylate (89):**

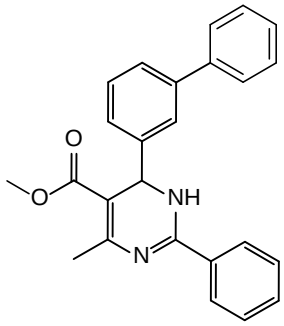



LC-MS (APCI+) *m/z* 805 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.92 (d, *J* = 9.0 Hz, 2H), 7.79 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.45-7.36 (m, 2H), 7.33 (s, 1H), 7.19-7.08 (m, 2H), 5.66 (s, 1H), 3.58 (s, 3H), 3.72 (s, 3H), 2.41 (s, 3H).

$^{13}$C NMR (75.5 MHz, $CDCl_3$), δ 170.1, 166.9, 160.2, 153.0, 149.9, 146.0, 133.6, 132.3, 130.4, 128.9, 127.8, 127.3, 127.0, 120.5, 120.2, 119.7, 118.6, 117.6, 116.4, 114.9, 55.9, 51.4, 29.7, 23.8.

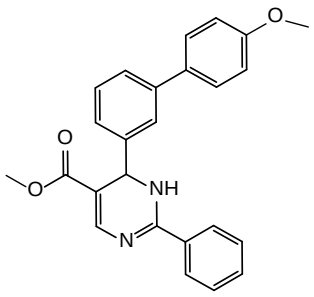
**Methyl 6-([1,1'-biphenyl]-3-yl)-4-methyl-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (90):**




LC-MS (APCI+) *m/z* 383 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.71 (d, *J* = 6.6 Hz, 2H), 7.62 (s, 1H), 7.56 (d, *J* = 9.6 Hz, 4H), 7.54-7.32 (m, 7H), 5.84 (s, 1H), 3.67 (s, 3H), 2.48 (s, 3H).

**Methyl-6-(4'-methoxy-[1,1'-biphenyl]-3-yl)-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (91):**

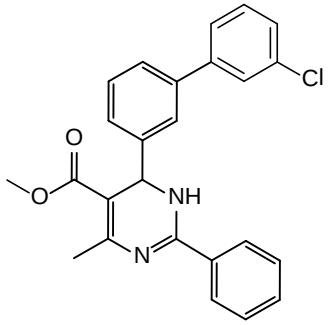



LC-MS (APCI+) *m/z* 413 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.68 (s, 1H), 7.56-7.48 (m, 3H), 7.40-7.26 (m, 3H), 6.74 (d, *J* = 8.1 Hz, 2H), 5.79 (s, 1H), 3.64 (s, 6H), 2.65 (s, 3H).

$^{13}$C NMR (75.5 MHz, $CDCl_3$), δ 170.2, 166.7, 153.8, 152.7, 149.6, 141.1, 136.4, 133.0, 132.3, 130.2, 129.4, 129.2, 128.4, 126.7, 124.6, 114.2, 57.2, 55.9, 51.7, 23.5.

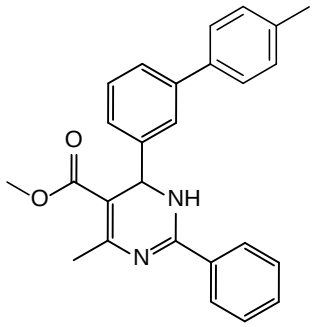
**Methyl 6-(3'-chloro-[1,1'-biphenyl]-3-yl)-4-methyl-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (92):**




LC-MS (APCI+) *m/z* 417 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.72 (d, *J* = 6.0 Hz, 2H), 7.59 (s, 1H), 7.53 (t, *J* = 9.0 Hz, 1H), 7.48-7.36 (m, 7H), 7.33 (s, 1H), 7.30 (t, *J* = 9.3 Hz, 1H), 5.85 (s, 1H), 3.68 (s, 6H), 2.45 (s, 3H).

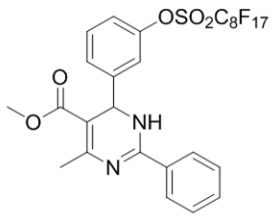
**Methyl 4-methyl-6-(4'-methyl-[1,1'-biphenyl]-3-yl)-2-phenyl-1,6-dihydropyrimidine-5-carboxylate (93):**




LC-MS (APCI+) *m/z* 397 $[M+1]^+$.

$^1$H NMR (300 MHz, $CDCl_3$), δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 4H), 7.42 (t, *J* = 9.3 Hz, 1H), 7.40-7.29 (m, 3H), 7.24 (s, 1H), 5.84 (s, 1H), 3.67 (s, 3H), 2.43 (s, 3H), 2.05 (s, 3H).

**Product 89**




```
 File  : C:\CHEM32\1\DATA\11-04-18\008-0401.D
le Name : FR-58
================================================================
 Operator   : B                              Seq. Line :   4
 Instrument : Instrument 1                    Location : Vial 8
tion Date   : 4/18/2011 4:00:49 PM                 Inj :   1
                                           Inj Volume : 4 µl
 Method     : C:\CHEM32\1\METHODS\GEMETHOD1.M
 changed    : 3/10/2011 9:35:54 PM by Z
ysis Method : C:\CHEM32\1\METHODS\CINCHONA.M
 changed    : 3/18/2011 4:19:30 PM
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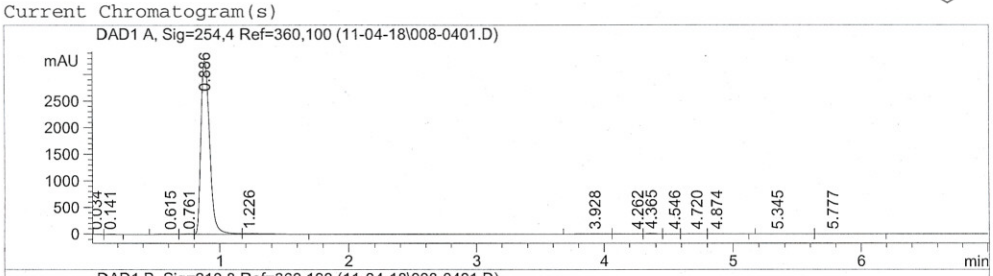
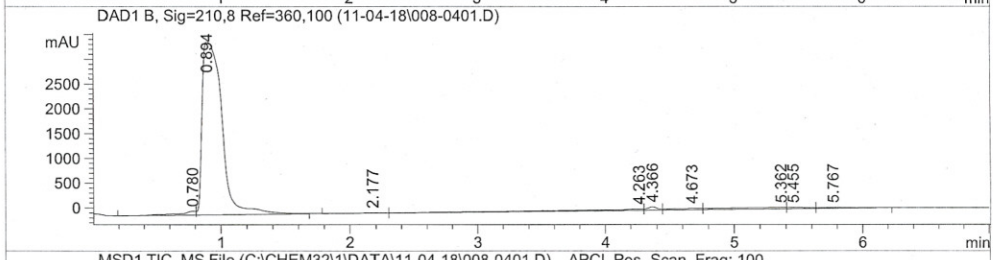
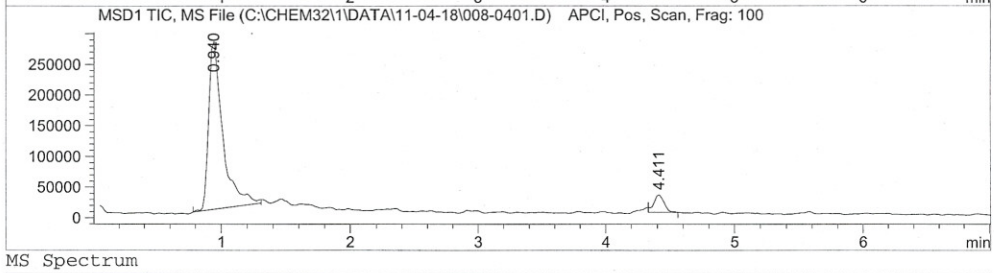
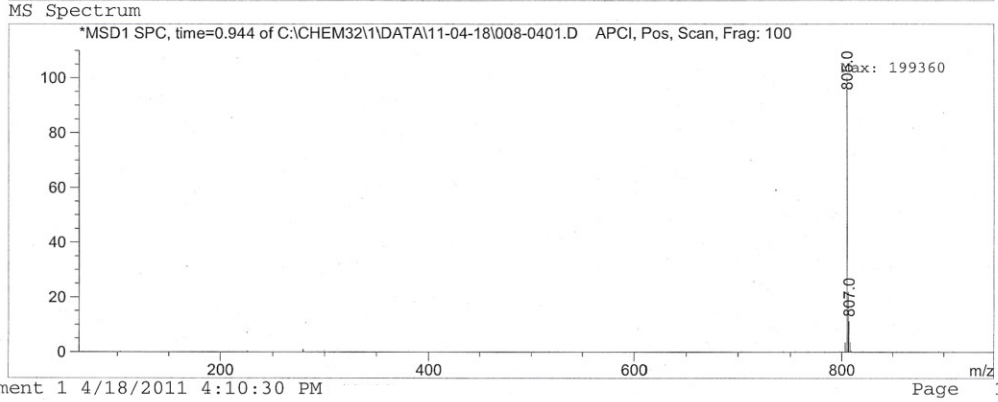
Current Chromatogram(s)



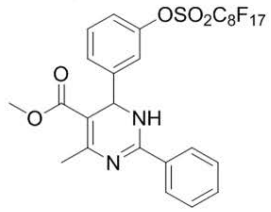

MS Spectrum



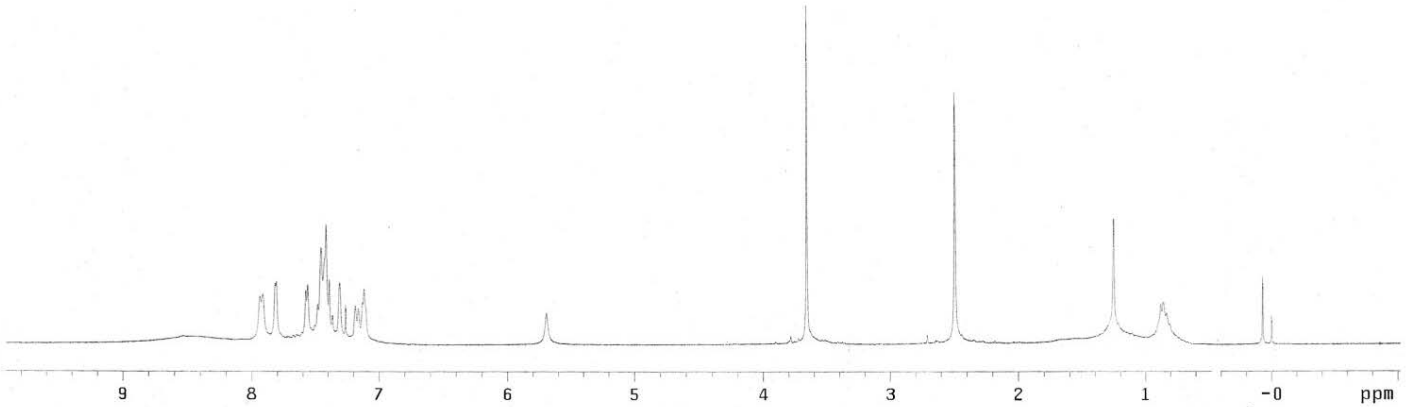
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266249 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 19 sec



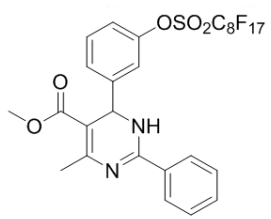

**89**



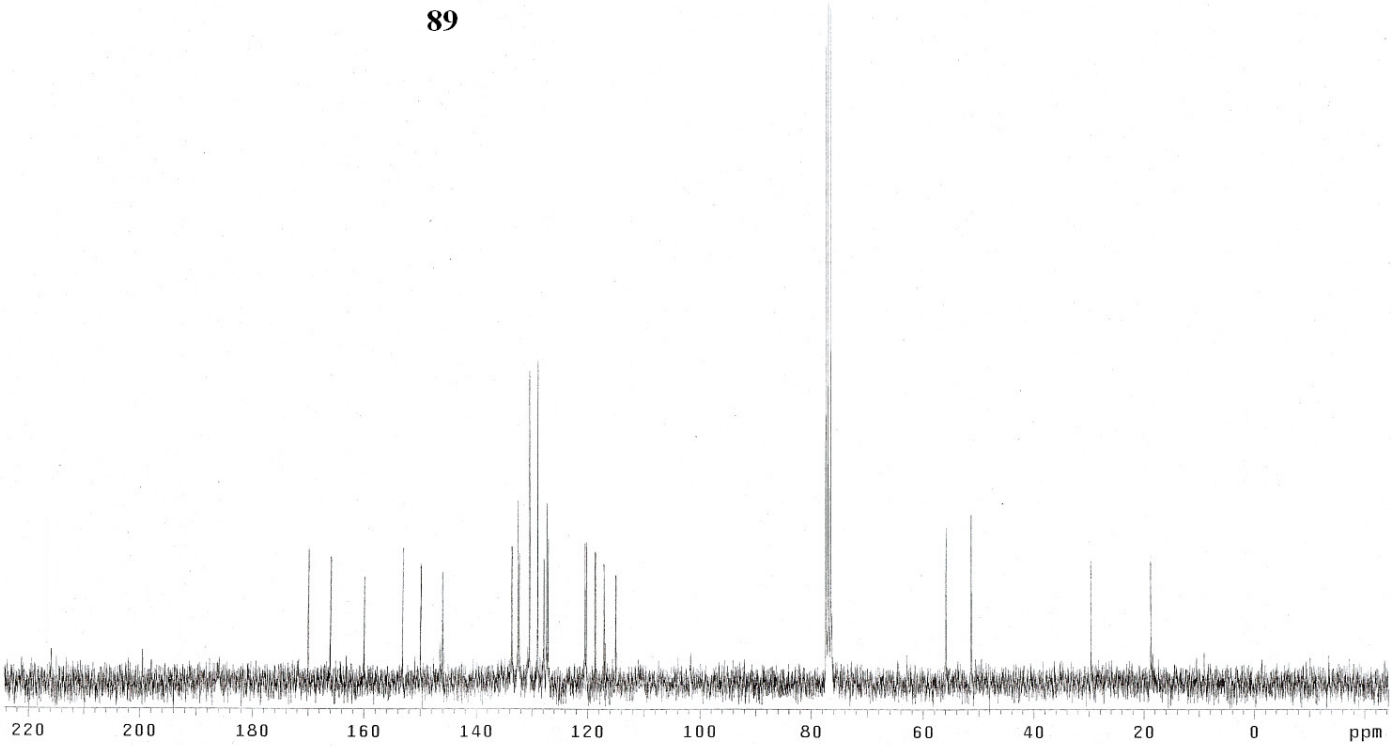
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

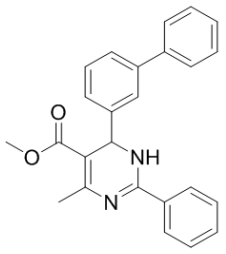
Pulse 75.9 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
3072 repetitions
OBSERVE C13, 75.4669010 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 48 min, 10 sec




**89**



**Product 90**

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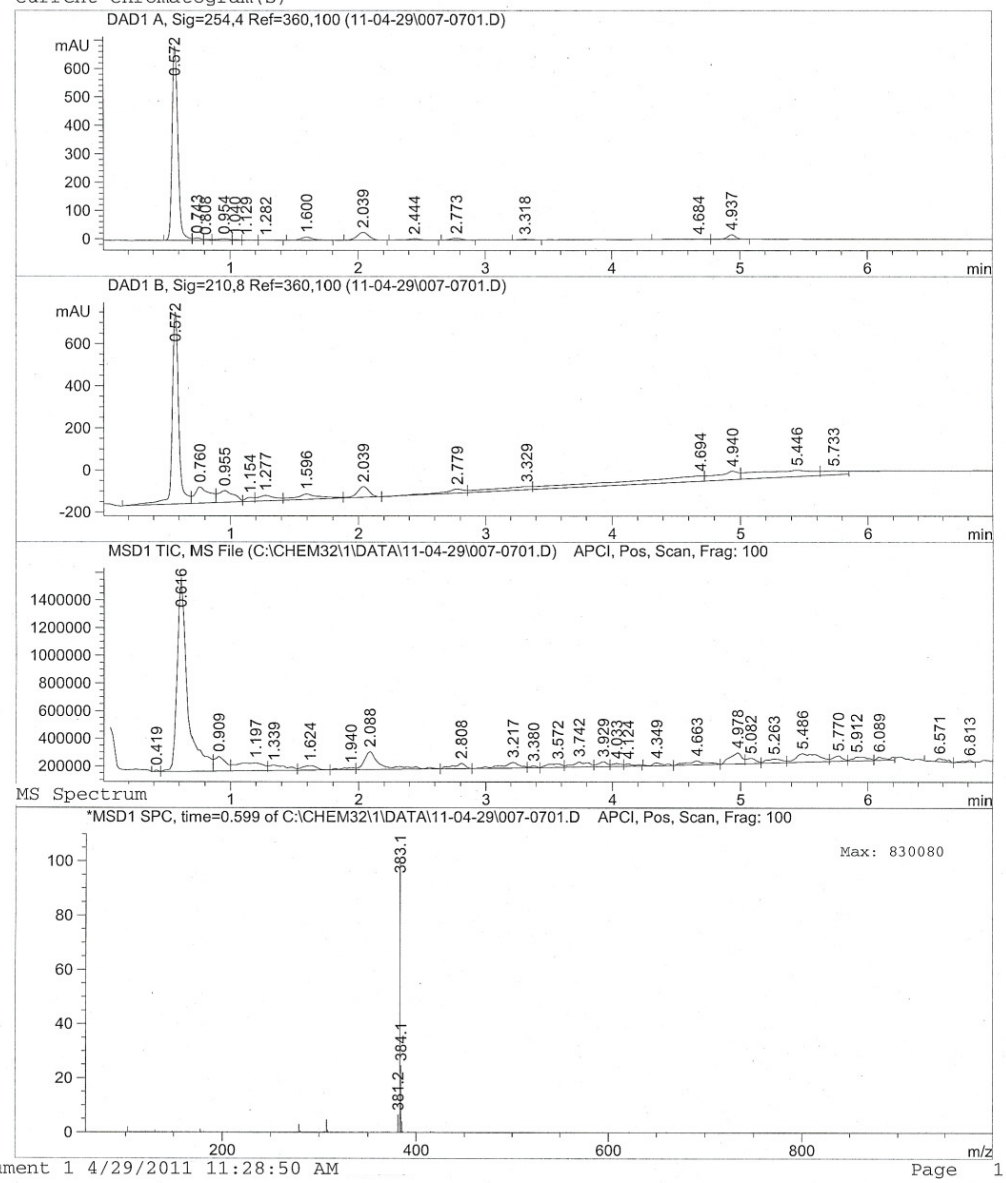
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-04-29\007-0701.D
Sample Name : L-S A2B1C5D2D
================================================================================
Acq. Operator   : B                                  Seq. Line :   7
Acq. Instrument : Instrument 1                        Location : Vial 7
Injection Date  : 4/29/2011 11:09:58 AM                  Inj :   1
                                                    Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
```

Current Chromatogram(s)

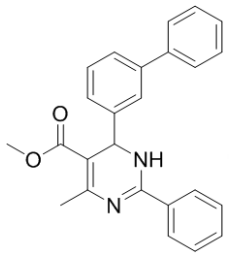



MS Spectrum

STANDARD 1H OBSERVE

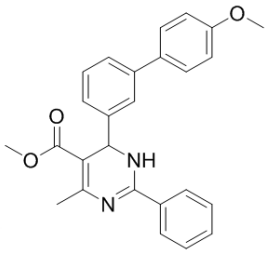
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266254 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 19 sec



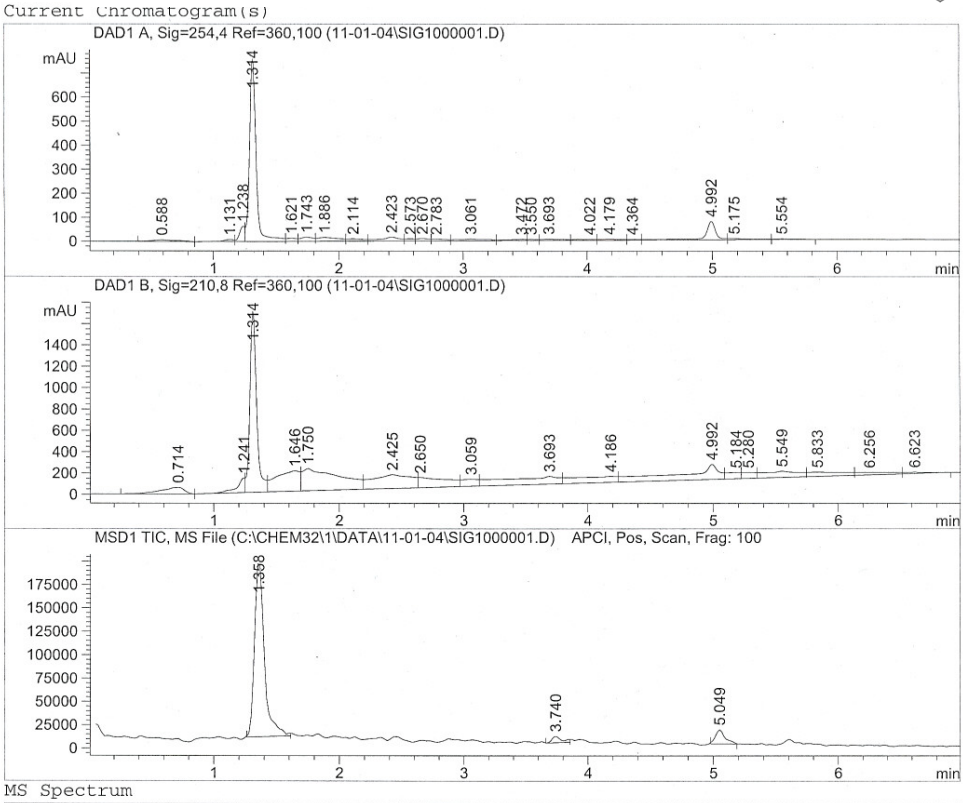

**90**

**Product 91**

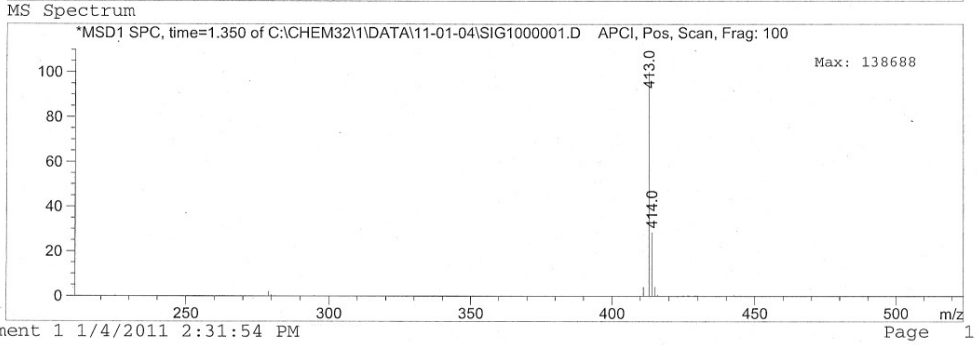



```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-01-04\SIG1000001.D
Sample Name : Suz Lib-S 412
==========================================================================
Acq. Operator   : B                                  Seq. Line :   1
Acq. Instrument : Instrument 1                        Location : Vial 5
Injection Date  : 1/4/2011 2:22:04 PM                      Inj :   1
                                                    Inj Volume : 4 µl
Acq. Method     : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 12/23/2010 11:36:52 AM by Z
Analysis Method : C:\CHEM32\1\METHODS\CINCHONA.M
Last changed    : 9/23/2010 6:12:44 PM by S
```

Current Chromatogram(s)



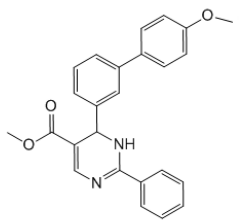

MS Spectrum



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.00[ sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266246 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 19 sec

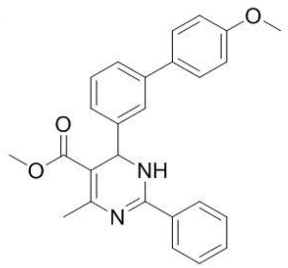



**91**

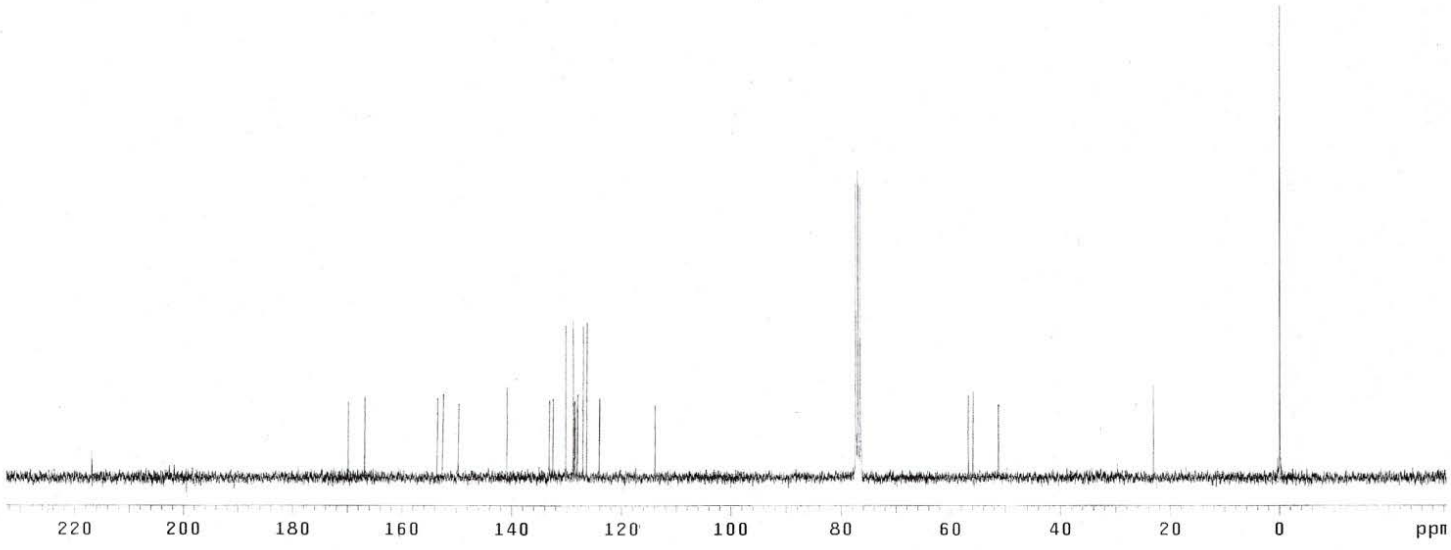
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

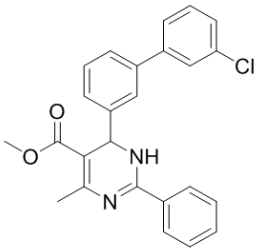
Relax. delay 2.000 sec
Pulse 67.8 degrees
Acq. time 1.815 sec
Width 20000.0 Hz
1530 repetitions
OBSERVE C13, 75.4669000 MHz
DECOUPLE H1, 300.1281260 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 1 hr, 45 min, 17 sec




**91**



**Product 92**




```
Print of all graphic windows
Data File  : C:\CHEM32\1\DATA\11-04-29\006-0601.D
Sample Name : L-S A2B1C5D2D
======================================================================
Acq. Operator   : F                              Seq. Line :   6
Acq. Instrument : Instrument 1                    Location : Vial 6
Injection Date  : 4/29/2011 11:01:25 AM              Inj :   1
                                                 Inj Volume : 4 µl
Method          : C:\CHEM32\1\METHODS\GEMETHOD1.M
Last changed    : 4/27/2011 11:04:42 AM by J
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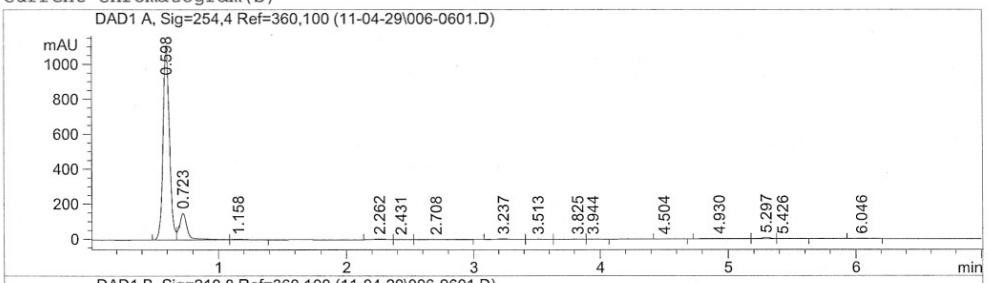
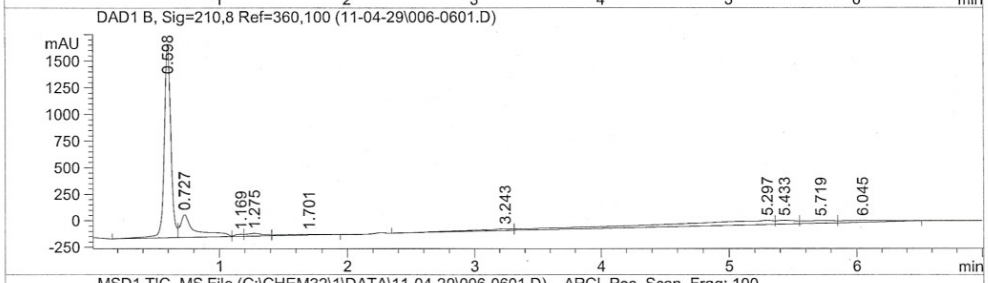
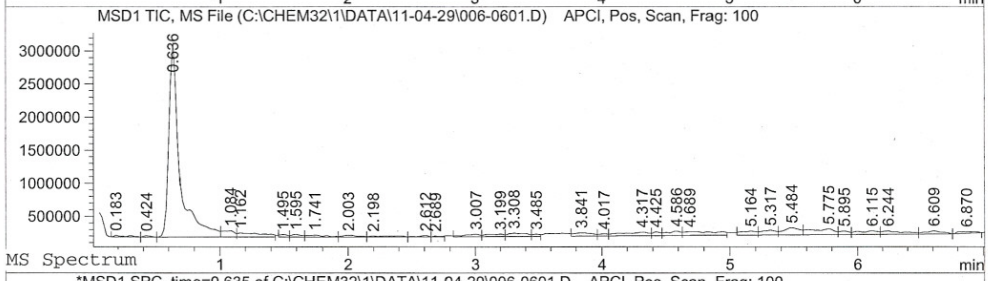
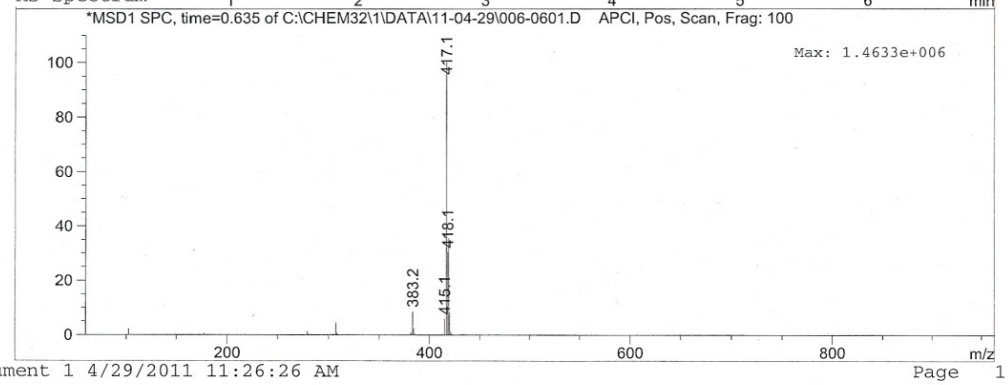
Current Chromatogram(s)




MS Spectrum



STANDARD 1H OBSERVE

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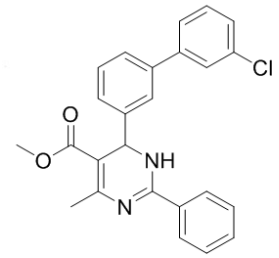
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
64 repetitions
OBSERVE H1, 300.1266246 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec




**92**

nt of all graphic windows
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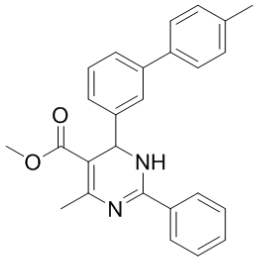
ple Name : Cycloa A5B1C6+D2 Suz FC Fr-17

**Product 93**




| | | | |
|---|---|---|---|
| . Operator | : Z | Seq. Line | : 1 |
| Instrument | : Instrument 1 | Location | : Vial 4 |
| ection Date | : 4/11/2010 6:44:48 PM | Inj | : 1 |
| | | Inj Volume | : 4 µl |
| . Method | : C:\CHEM32\1\METHODS\GEMETHOD1.M | | |
| t changed | : 4/9/2010 2:34:27 PM by J | | |
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| t changed | : 2/12/2010 10:11:02 AM by Z | | |

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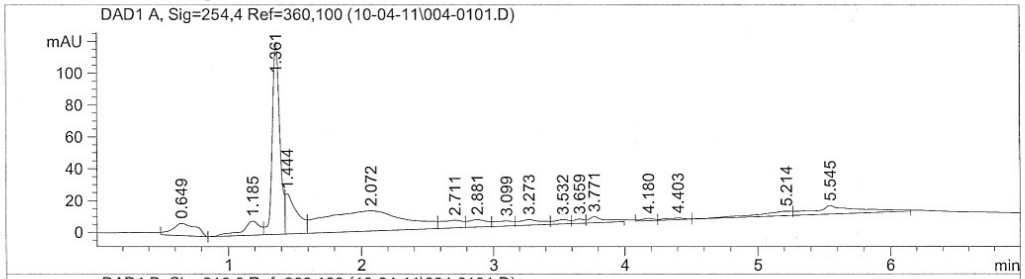
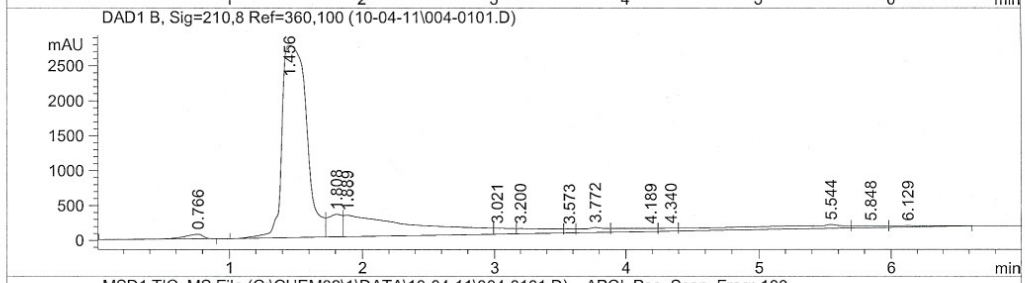
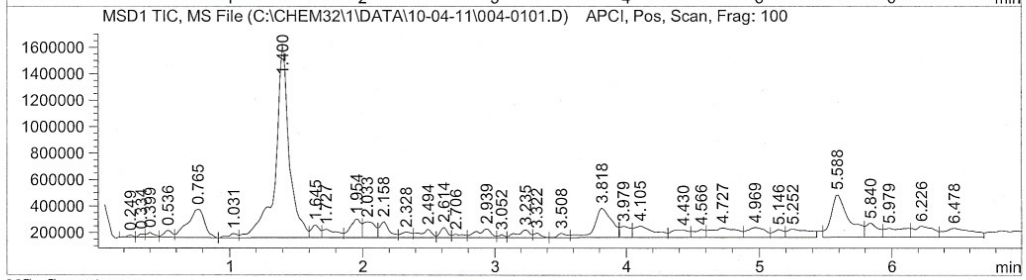
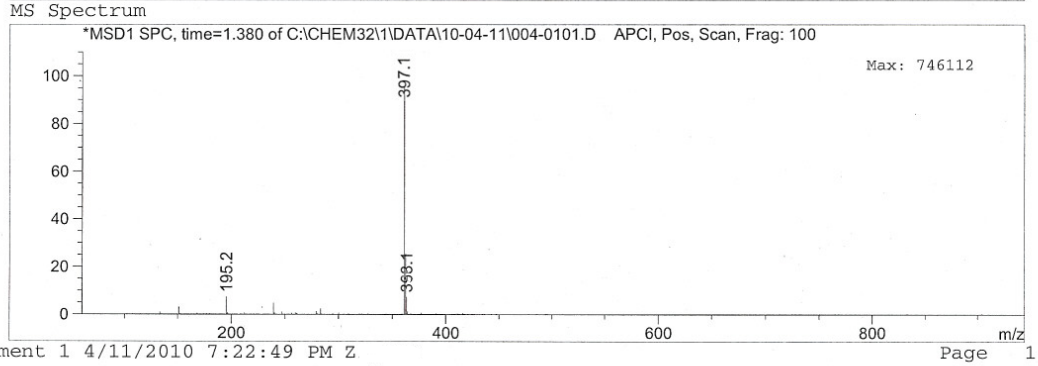


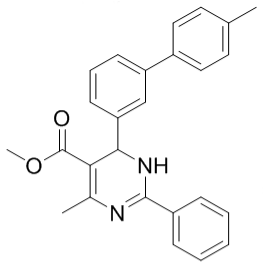

MS Spectrum



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300BB "Mighty300"

Relax. delay 1.000 sec
Pulse 43.4 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.1266194 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec

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