2015

Biginelli Synthesis And Characterization Of Potentially Anti-proliferative Dihydropyrimidinone Thione Analogs

Timothy K. Summers

BIGINELLI SYNTHESIS AND CHARACTERIZATION OF POTENTIALLY ANTI-PROLIFERATIVE DIHYDROPYRIMIDINONE THIONE ANALOGS

Timothy K. Summers

COLUMBUS STATE UNIVERSITY

BIGINELLI SYNTHESIS AND CHARACTERIZATION OF POTENTIALLY ANTI-PROLIFERATIVE DIHYDROPYRIMIDINONE THIONE ANALOGS

A THESIS SUBMITTED TO

THE HONORS COLLEGE AT COLUMBUS STATE UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE WITH HONORS OF

BACHELORS OF ARTS

DEPARTMENT OF CHEMISTRY

BY

TIMOTHY K. SUMMERS

COLUMBUS, GEORGIA

2015

Biginelli Synthesis and Characterization of Potentially Anti-Proliferative Dihydropyrimidinone Thione Analogs

by

Timothy K. Summers

A Thesis Submitted to the Honors College at Columbus State University in Partial Fulfillment of the Requirements for the Degree with honors of Bachelors of Arts

in

Chemistry

College of Letters & Sciences

Columbus State University

Thesis Advisor _____ Date 5/5/2015

Dr. Renat Khatmullin

Committee Member _____ Date 5/5/2015

Dr. Samuel Abegaz

Honors College Dean _____ Date 5/5/15

Dr. Cindy Ticknor

ABSTRACT

Advisors Drs Kenneth L. Smith and Renat Khatmullin

It is well established that the class of compounds known as dihydropyrimidinones (DHPMs) exhibits a wide range of biological activity due to their constituent stereogenic centers. For this reason, there have been many years of ongoing research to find an efficient and practical method for DHPM synthesis. An often employed and proven method is the Biginelli Condensation Reaction. One facet of this reaction's promise comes from the fact that it can be carried out under an array of chemical conditions; however, it is not at all without complications. While understanding the 'solvent-free' mechanism and finding a cheap catalyst are of some concerns for this particular approach, the major problem is finding a technique which gives high product yields, has limited drawbacks, and is safe for the environment. Therefore, the aim of the study was not only to create DHPM thione derivatives, but also to find an efficient and friendly method for their synthesis.

What we found is that one-pot, solvent-free conditions will, in fact, successfully yield the desired products. Though, it should be noted that an unfortunate lack of documentation brought about our inability to accurately determine the overall percent recovered, which was one of the main objectives; however, the product yield seemed generous in terms of what was physically observable. In addition to a successful solvent free synthesis, we found that a cost friendly catalyst, zinc chloride ($ZnCl_2$), was a viable reagent for these types of reactions.

It is important to note here that the Biginelli Condensation Reaction mechanism typically involves three primary components: (i) β-ketoester; (ii) an aryl aldehyde; (iii) urea or thiourea analog. Our goal was to carry out the reaction using a variety of aryl aldehydes, thus a series of compounds differing only at that particular moiety were synthesized. The aforementioned technique of choice appeared to be successful in each product's formation, with the exception of one. Melting point analysis (MP), infrared spectroscopy (IR), gas chromatography – mass spectroscopy (GC-MS), and nuclear magnetic resonance spectroscopy (NMR) were each used to investigate the products' congruence with their hypothesized structures. We report those findings along with the respective accuracies.

INDEX WORDS: Biginelli, dihydropyrimidinones, DHPMs, Biginelli Condensation

TO MY BIGGEST SUPPORTER

My mom, Suzann Hunter, who has encouraged me, who has inspired me, and most importantly, who has never stopped believing in me. Without her, none of this is possible.

ACKNOWLEDGMENTS

I would like to thank:

My advisor, Dr. Kenneth L. Smith, for presenting me with the opportunity to carry out this research, which has been highly relevant to my future goals, and also for both watching over me and guiding me as the experiments were conducted.

My advisor, Dr. Renat R. Khatmullin, for providing his help and insight as I continued with the synthesis and characterization of my compounds.

Dr. Floyd R. Jackson for advising me over the years, both in my classes and life. Your encouragement and belief in me means more than you know. Thank you for all the help.

Dr. Cindy S. Ticknor for keeping me on track for completing my honors requirements, and for understanding, as well as considering, my circumstances when making exceptions for me. Thank you for allowing me to graduate with honors.

Finally, all of my chemistry professors (Dr. Samuel Abegaz, Dr. Daniel W. Holley, Dr. Zewdu Gebeyehu, Dr. Rajeev B. Dabke, and Dr. Anil Banerjee) who have taught me everything I have needed to be a successful chemistry graduate, and who have been positive supporters of my goals and pursuits.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

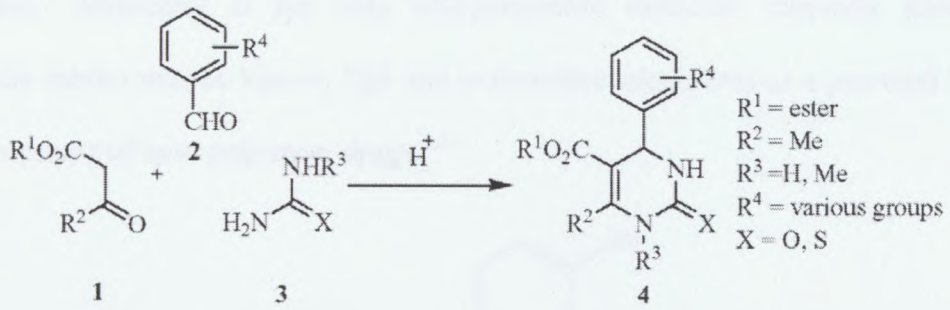
LIST OF TABLES

Chapter I

Introduction

1.1.1 Dihydropyrimidinones (DHPMs)

Dihydropyrimidinones, or DHPMS, are a class of compounds resulting from the condensation of ethyl acetoacetate, an aromatic aldehyde, and urea or thiourea analog, usually in protic conditions, which leads to the synthesis of reduced pyrimidines (Scheme 1.1).[1,4] The DHPM products of this multicomponent Biginelli reaction, also known as Biginelli compounds[1], have been identified as 3,4-dihydropyrimidin-2(1H)-ones.[2,4] A wide variety of catalysts and reaction modifications have been employed to develop the existing array of DHPMs, their thione analogs, and their heterocyclic derivative compounds.[3,4] All have gained increasing relevance due to their wide range of applications, particularly in the area of medicine.[3,4,8] It has been noted by Kawaljit and Kamaljit Singh, that since the first review by Kappe et al, which appeared exactly 100 years after the seminal report by Pietro Biginielli, there has been unprecedented research activity on the chemistry and biology of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs).[1]



Scheme 1.1 *General Reaction Scheme for Formation of Dihydropyrimidinones*[1]

1.1.2 Importance of DHPMs

Up until the early 1980's, the properties of this Dihydropyrimidinone scaffold was unexplored, until it was realized that these intrinsically asymmetric DHPMs are structural analogs (aza analogs) of the well-known 4-aryl- 1,4-dihydropyridines (DHPs), which are

calcium channel modulators of nifedpine type.[1,4,8] Interest shifted to the DHPM pharmacological profile not only to understand their role as calcium channels modulators, but also to gain insight into their molecular interaction at the receptor level.[1]

Currently, it has been found that DHPM heterocycles exhibit a wide range of pharmacological properties including antiviral, antibacterial, antioxidant, analgesic, anticonvulsant, anti-coagulant, anti-inflammatory, and anti-HIV activies.[2-6,8] When properly functionalized, DHPM analogs can also act as orally active anti-hypersensitive agents and α_{1a} adrenoceptor-selective antagonists.[3] Perhaps an even more important anti-proliferative DHPM derivative is the simply structured Monastrol (Figure 1.1). Monastrol is a cell-permeable, mitotic kinesin inhibitor that easily crosses the cell membrane and blocks normal bipolar spindle assembly formation in mammalian cells leading to cell cycle arrest.[2,4] Bignielli adducts of this type affect mitosis independently of tubulin binding through a mechanism also observed in drugs like taxanes, vinca alkaloids, and epothilones.[2] Monastrol is the only cell-permeable molecule currently known to specifically inhibit mitotic kinesin Eg5 and is therefore considered as a potential lead in the development of new anticancer drugs.[5,11]

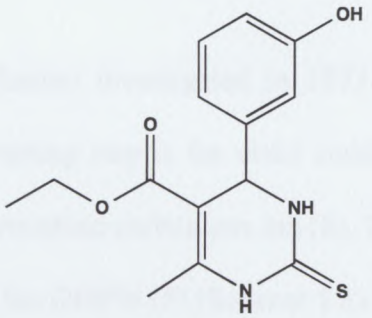
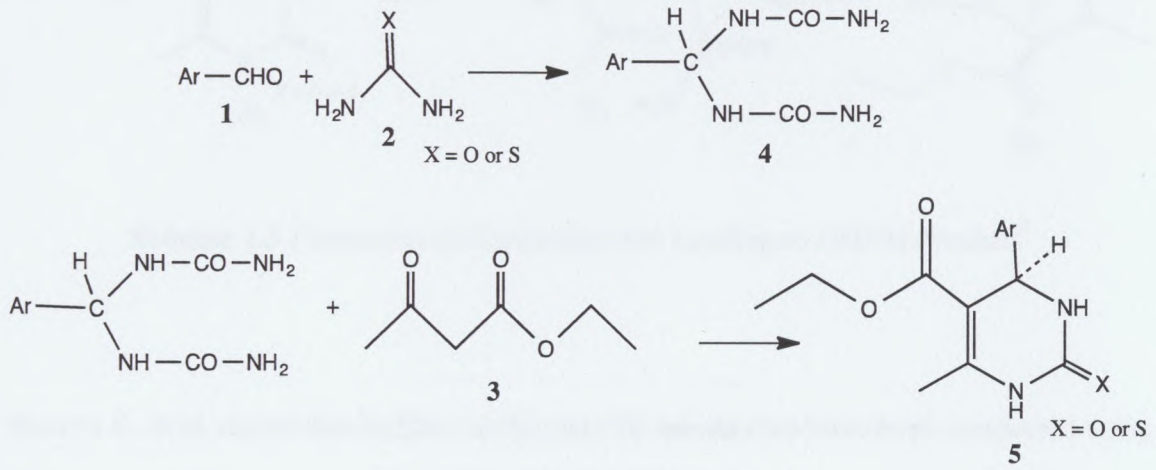


Figure 1.1 *Monastrol*

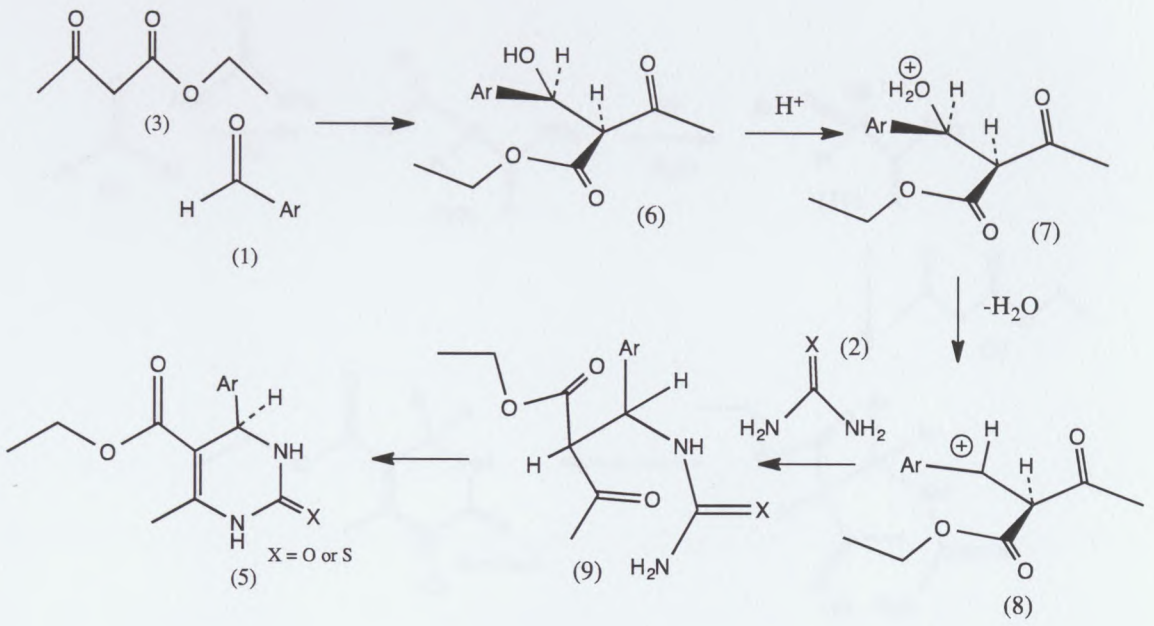
1.1.3. Theory of Reaction Mechanism

It is reported by Bhavya K. et al. that there have been several research groups who have worked on mechanistic aspects of DHPM synthesis by Biginelli Reaction[4]. The first reported mechanism was proposed in 1933 by Folkers K. and Johnson T.B.[4] They suggest that the aryl aldehyde (1) first reacts with urea or thiourea analog (2) to form benzalbisureide (4), which continues reacting with the ethyl acetoacetate component (3) to afford the DHPM product (5) (Scheme 1.2).[4]



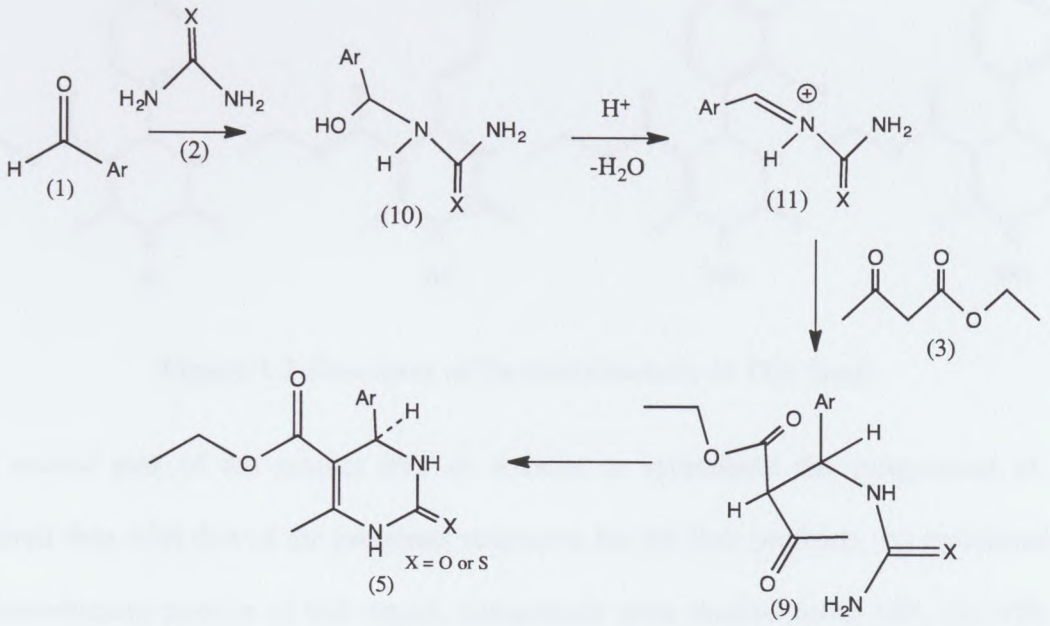
Scheme 1.2 *Formation of Benzalbisureide Leading to DHPM Product*[4]

The initial mechanism was further investigated in 1973 by Sweet and Fissekis[4] who suggested that the rate determining step is the aldol condensation of ketoester with the aldehyde, that leads to an intermediate carbonium ion (8). The reaction of (8) with urea or thiourea leads to formation of the DHPM (5) (Scheme 1.3).[4]



Scheme 1.3 *Formation of Carbonium Ion Leading to DHPM Product*[4]

Bhavya K. et al. report that further studies into the mechanism have been conducted using ^{1}H-NMR and ^{13}C-NMR by Kappe C.O. et al.[4] They conclude that rather than the initial step involving an aldol condensation or carbenium ion, the mechanism actually proceeds first with the condensation of benzaldehyde and urea giving an N-acyliminium ion intermediate (11) which finally reacts with ethyl acetoacetate to afford the DHPM product (Scheme 1.4).[4]



Scheme 1.4 *Formation of N-acyliminium Leading to DHPM Product*[4]

1.1.4. The Aim of Our Study

As the mechanism of the reaction is still under investigation, it was subsidiary to the goals of our investigation. Objectives were to not only successfully prepare four separate 3,4-dihydropyrimidin-2(1H)-thiones differing about the C-4 position aryl aldehyde moiety, but also to add confirmation to the existing body of knowledge on the synthesis of this class of compounds. In our study we examined the efficiency of the one-pot, three-component Biginelli Condensation Reaction under solvent-free conditions using a cost-friendly catalyst. The first part of our experiment is aimed at simply synthesizing the DHPMs shown below (Figure 1.2) under the aforementioned settings.

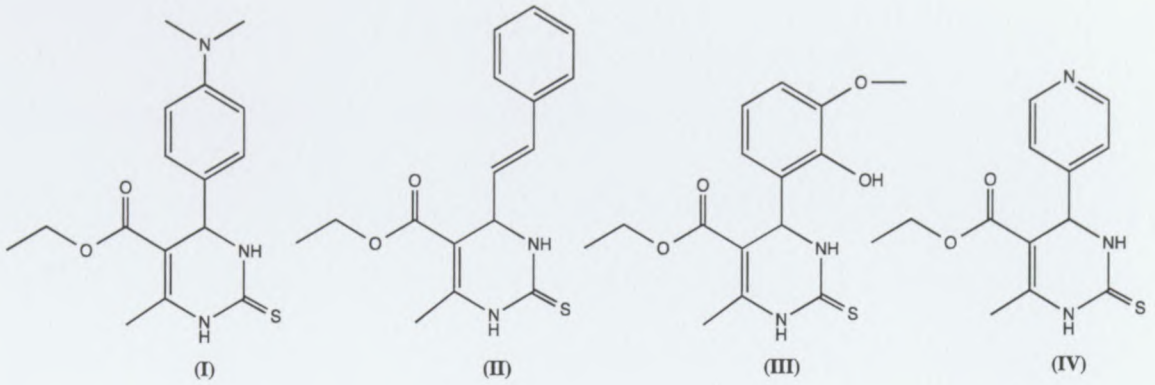


Figure 1.2 *Structures of Desired Products in This Study*

The second part of the project was an attempt to investigate the congruence of the acquired data with that of the proposed structures for the four products. As mentioned in the introductory portion of this report, compounds were studied using MP, GC-MS, IR spectroscopy, and ^{1}H-NMR spectroscopy. The findings for each of these analyses are discussed in the second chapter of this report.

Chapter II

Solvent Free Synthesis of DHPM Thione Analogs

2.1.1 Current Strategies for Dihydropyrimidinones

While is has been studied for more than a century, A.N. Dadhania and group claim that the best-known and most useful method for dihydropyrimidinone synthesis is that of the classical Biginelli Reaction.[6] This classic method involved heating a mixture of three components which included β-ketoester, aldehyde, and urea in ethanol containing a catalytic amount of HCl.[8] According to A. Debache et al. the major drawbacks to this protocol are both the use of a strong acid and the low yields which result when substituted aromatics and aliphatic aldehydes are incorportated.[8] Since this 1893 reaction's debut, extensive exploration has been conducted into this procedure, where the employment of various catalyst and reaction conditions are carried out in hopes of notable improvements.[3,5,6,8,11]

Exemplary of these sought advancements is the compendium of catalyst that currently exists which includes Lewis and protic acid promoters such as LiBr, $MgBr_2$, CaF_2, $FeCl_3 \cdot 6H_2O$, $Mn(OAc)_3$, $InBr_3$, ZnI_2, $CdCl_2$, H_3BO_3[(8,4)], $PhB(OH)_2$, CuI, H_2SO_4, $ZnCl_2$, $SnCl_2$, $CuCl_2$, $CoCl_2$, $NiCl_2$, I_2, TMSI, $Yb(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$, $Cu(NTf)_2$, $Ni(NTf)_2$, $Yb(NTf)_2$, $Ce(NO)_3 \cdot 6H_2O$, $CeCl_3 \cdot 7H_2O$, $RuCl_3$, $ZrCl_4$, $LiBr_2$, $Co(OAc)_2$, *p*-TSA, $Ag_3PW_{12}O_{40}$, HBF_4[(3,4)], and bases like NH_4Cl or $KHSO_4$.[(3)] A. Debache et al. report a pronounced effect is seen in methods using metal salts with non-nucleophilic anions such as $LiClO_4$, $CuSO_4 \cdot 5H_2O$, $Cu(OTf)_2$, $Al(HSO_4)$, and trimethylsilyl triflate. Additionally they assert that the Biginelli reaction is accelerated by various procedures involving heteropoly acids, silica sulfuric acid, and ferric chloride/tetraethyl orthosilicate.[8]

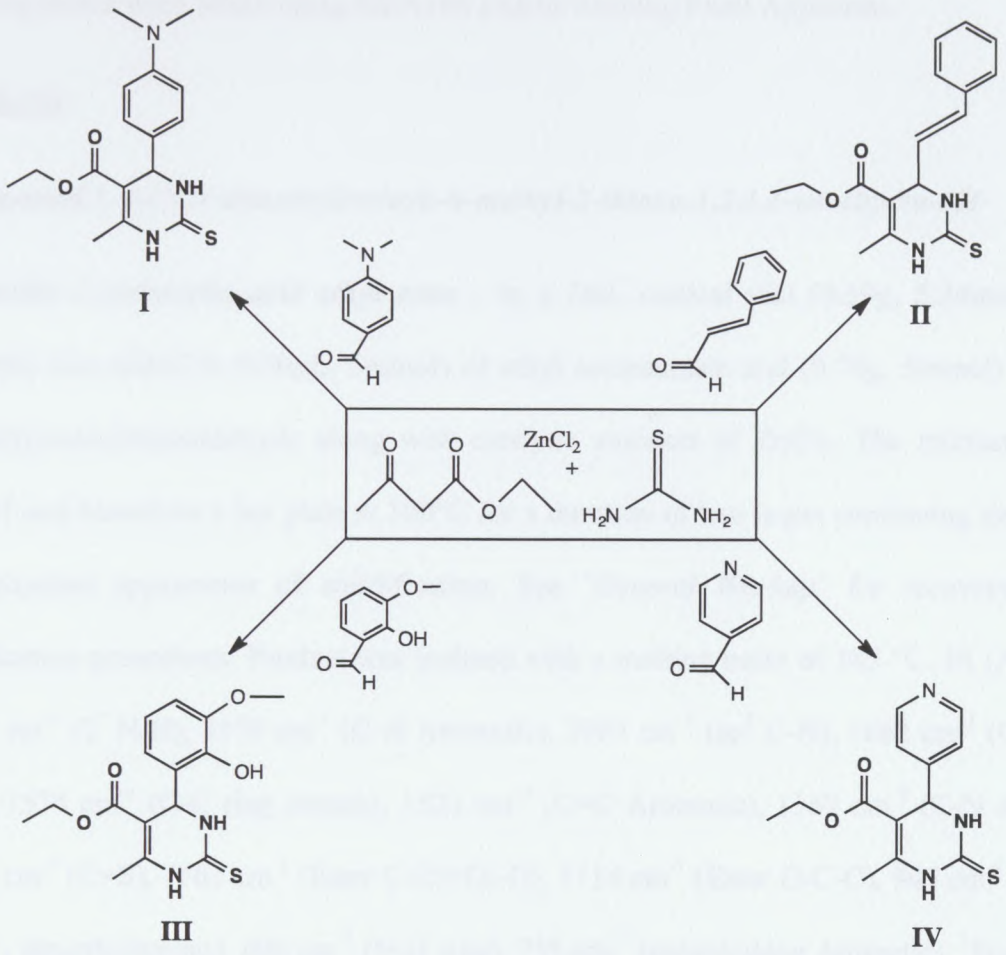
Though it seems much progress has been made with respect to the array of listed catalyst, there are many drawbacks still plaguing these reactions. Expensive catalyst, high temperatures, prolonged reaction times, corrosive reagents, low yields, laborious work up procedures, and large amounts of toxic wastes are some of the issues that have been noted to accompany current techniques. A.N. Dadhania et al. assert that these disadvantageous aspects restrict the practical synthetic implementation of this type of chemistry.[3,6-8]

While the search for a high yielding, solvent-free reaction that incorporates a friendly catalysts is still underway[3,8], other environmentally conscious routes have gained notable attention in recent years. These routes included the use of microwave irradiation (MWI) and the use of ionic liquids (ILs).[5-7] V. Srivastava reports ILs as being easily modifiable due to their tunable physicochemical properties which can be tailored to specific reactions, while A.N. Dadhania et al. point out that ILs polar nature and ionic characteristics allow them to couple efficiently with microwaves.[6,7] The latter assertion explains why microwave/ionic liquid (MW/ILs) may be used more effectively in DHPM synthesis[6], and it is noted that various groups have already investigated (MW/ILs) in different types of organic reactions.[7] With all of these findings in mind, our study focuses on simply carrying out an eco-friendly procedure, free from solvents and using a cost-friendly catalyst.

2.1.2 Reactions Involved in This Study

In our experiment we study the formation of DHPM products that, as mentioned, vary solely about the aldehyde moiety. The catalyst, $ZnCl_2$, the β-ketoester, ethyl acetoacetate, and the thiourea component are constant through each reaction. In compounds I-IV we incorporate Para-dimethylaminobenzaldehyde, trans-cinnamaldehyde, ortho-vanillin, and

4-pyridinecarboxaldehyde, respectively, in our attempt to obtain the shown products (Scheme 2.1)



Scheme 2.1 *Reactions Involved in the Formation of Intended Products*

2.2 Experimental Section

General Methods:

All chemicals were obtained from Sigma Aldrich and used without any further purification. ^{1}H-NMR spectra were obtained on Anasazi Eft-60 NMR Spectrometer. Chemical shifts in NMR analysis were scaled relative to tetramethylsilane (TMS) and

reported in parts per million (ppm). GC-MS spectra were measured on Shimadzu GC-MS. IR spectra were obtained on Perkin Elmer Spectrum 100 FT-IR Spectrometer and melting points were found using MPA160 Digital Melting Point Apparatus.

Synthesis:

Compound I. ***4-(N,N-dimethylaminyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester*** - In a 5mL conical vial (0.39g, 5.2mmol) of thiourea was added to (640µL, 5mmol) of ethyl acetoacetate and (0.70g, 5mmol) of p-dimethylaminobenzaldehyde along with catalytic amounts of $ZnCl_2$. The mixture was stirred and heated on a hot plate at 100°C for a duration of two hours continuing through the physical appearance of solidification. See '*General Workup*' for recovery and purification procedures. Product was isolated with a melting point of 185 °C. IR (ATR): 3323 cm^{-1} (2° N-H), 3170 cm^{-1} (C-H Aromatic), 2984 cm^{-1} (sp^3 C-H), 1662 cm^{-1} (C=O), 1591-1575 cm^{-1} (C-C ring stretch), 1523 cm^{-1} (C=C Aromatic), 1362 cm^{-1} (C-N alkyl), 1285 cm^{-1} (C=S), 1163 cm^{-1} (Ester C-C(=O)-O), 1114 cm^{-1} (Ester O-C-C), 945 cm^{-1} (C-N alkyl - dimethylamino), 806 cm^{-1} (N-H wag), 755 cm^{-1} (out-of-plane Aromatic). ^{1}H-NMR ($CDCl_3$): δ 7.47-7.18 (m, 2H, Ar), 6.96-6.69 (m, 2H, Ar), 5.45 (s, 1H), 4.26 (q, 2H, J = 7.8Hz, CH_2), 3.25 (s, 1H), 3.10 (s, 6H, N(-CH_3) x 2), 2.51 (s, 3H, CH_3), 1.36 (t, 3H, J = 7.8Hz, CH_3). EI: m/z 319 [M^+ Calculated for $C_{16}H_{21}O_2N_3S^+$].

Compound II. ***4-(2E)-3-phenyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester*** - In a 5mL conical vial (0.39g, 5.2mmol) of thiourea was added to (640µL, 5mmol) of ethyl acetoacetate and (630µL, 5mmol) of trans-cinnamaldehyde along with catalytic amounts of $ZnCl_2$. The mixture was stirred and

heated on a hot plate at 100°C for a duration of two hours continuing through the physical appearance of solidification. See '*General Workup*' for recovery and purification procedures. Product was isolated with a melting point of 80 °C-83 °C. IR (ATR): 3211-3201 cm^{-1} (2° N-H, Aromatic C-H), 2958 cm^{-1} (sp^3 C-H), 1646 cm^{-1} (E-alkene C=C), 1586 cm^{-1} (C=O), 1362 cm^{-1} (C-N alkyl), 1256 cm^{-1} (C=S), 1195-1164 cm^{-1} (Ester C-C(=O)-O), 1137 cm^{-1} (Ester O-C-C), 783 cm^{-1} (Aromatic), 694 cm^{-1} (E-alkene =C-H). ^{1}H-NMR ($CDCl_3$): δ 7.46-6.28 (m, 5H), 2.66-1.97 (m, 6H), 1.00 (s, 5H), 0.90 (s, 3H). EI: m/z 366 [M^+ Calculated for $C_{16}H_{18}O_2N_2S^+$].

Compound III. ***4-(2-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester*** - In a 5mL conical vial (0.38g, 5.1mmol) of thiourea was added to (640μL, 5mmol) of ethyl acetoacetate and (0.76g, 4.9mmol) of O-vanillin along with catalytic amounts of $ZnCl_2$. The mixture was stirred and heated on a hot plate at 100°C for a duration of two hours continuing through the physical appearance of solidification. See '*General Workup'* for recovery and purification procedures. Product was isolated with a melting point of 222 °C. IR (ATR): 3413cm^{-1} (Intermolecular OH-methoxy), 3149 cm^{-1} (2° N-H), 2998 cm^{-1} (sp^3 C-H), 1676 cm^{-1} (C=O), 1592-1574 cm^{-1} (C-C ring stretch), 1517 cm^{-1} (C=C Aromatic), 1370 cm^{-1} (C-N alkyl), 1259 cm^{-1} (C=S), 1234 cm^{-1} (Asymmetric C-O-C) 1192-1153 cm^{-1} (Ester C-C(=O)-O), 1111 cm^{-1} (Ester O-C-C), 1033 cm^{-1} (Symmetric C-O-C), 858 cm^{-1} (N-H wag), 772 cm^{-1} (out-of-plane Aromatic). ^{1}H-NMR (DMSO): δ 10.28 (s, 1H), 9.57 (s, 1H), 9.02 (s, 1H), 6.95-6.43 (m, 3H, Ar), 5.13 (d, 1H), 4.08 (q, 2H, J = 7.8Hz, CH_2), 3.71 (s, 3H), 3.36 (s, 2H), 2.32 (s, 3H), 1.17 (t, 3H, J = 7.8Hz, CH_3). EI: m/z 322 [M^+ Calculated for $C_{15}H_{18}N_2O_4S^+$].

Compound IV. ***4-(4-pyridine)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester*** - In a 5mL conical vial (0.38g, 5.1mmol) of thiourea was added to (640µL, 5mmol) of ethyl acetoacetate and (470µL, 4.9mmol) of 4-pyridinecarboxaldehyde along with catalytic amounts of $ZnCl_2$. The mixture was stirred and heated on a hot plate at 100°C for a duration of two hours continuing through the physical appearance of solidification. See '*General Workup'* for recovery and purification procedures. Product was isolated with a melting point of 187 °C. IR (ATR): 3336cm^{-1} (2° N-H), 2965 cm^{-1} (sp^3 C-H), 1661 cm^{-1} (C=O), 1462-1428 cm^{-1} (C-C, C-N ring stretch), 1373 cm^{-1} (C-N alkyl), 1339 cm^{-1} (C-N Aromatic), 1278 cm^{-1} (C=S), 1185 cm^{-1} (Ester C-C(=O)-O), 1107 cm^{-1} (Ester O-C-C), 825 cm^{-1} (N-H wag), 767 cm^{-1} (Aromatic). ^{1}H-NMR (DMSO): δ 10.53 (s, 1H), 9.8 (s, 1H), 8.81-8.50 (m, 2H, Ar), 7.78-7.18(m, 2H, Ar), 5.28 (d, 1H), 4.11 (q, 2H, J = 7.2Hz, CH_2), 3.74-3.31 (m, 1H), 2.37 (s, 3H), 1.17 (t, 3H, J = 7.2Hz, CH_3). EI: m/z 277 [M^+ Calculated for $C_{13}H_{15}N_3O_2S^+$].

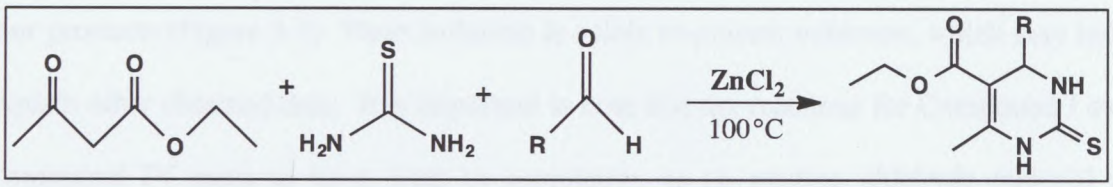
General Workup Procedure:

A mixture of deionized water and ethanol was first used to dissociate the solidified products into a filterable precipitate, noting that some compounds only required water. Masses that successfully dissociated as precipitate were then vacuum filtrated using additional portions of ice-cold ethanol and water. Products not responding to the ethanol mixture were extracted into either ethyl acetate or ether followed by the evaporation of the organic solvent, which led to the formation of a solid or oil. Solids were filtered using ice-cold ethanol and water as before. To the oils, more water and ethanol were added at elevated temperatures as well as while the mixture cooled until precipitate formed, at

which point the product was vacuum filtrated with more washes of cold ethanol and water.

2.3 Results and Discussion

The 3,4-dihydropyrimidin-2(1H)-thiones were synthesized successfully with the exception of one product. Compound I (*4-(N,N-dimethylaminyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester)*, Compound III (*4-(2-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester)*, and Compound IV (*4-(4-pyridine)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester)*, were synthesized via a one-pot, three-component reaction of the Biginielli type, under solvent free conditions using $ZnCl_2$ as the catalyst, as shown in Scheme 2.2. Compound II (*4-(2E)-3-phenyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-4H-pyrimidin-5-carboxylic acid ethyl ester)* was unobtainable as indicated by various analytical techniques, though it was carried out under the same conditions.



Scheme 2.2 *General Synthetic Procedure for DHPM Synthesis*

Table 2.1 Synthesis Data for DHPM Thione Analogs Using Varied Aldehydes

Compound	-R	Reaction Time (min)	MP/°C
I	4-$(CH_3)_2N$-C_6H_4	120	185
II	1E-2-Phenyl	120	80 – 83
III	2-MeOH-3-MeO-C_6H_3	120	222
IV	4-Pyridyl	120	187

Reaction Temperature = 100 °C

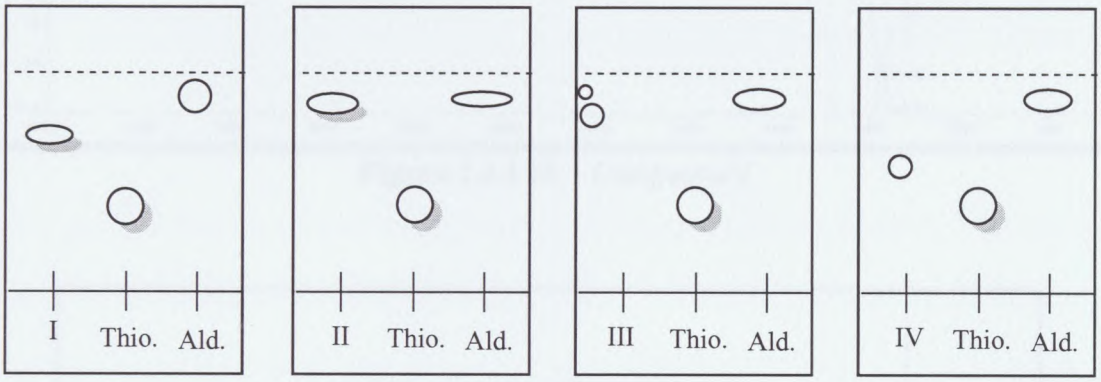


Figure 2.1 *TLC sketches of Compounds I-IV*

Reported are the general sketches representative of the respective TLC analyses for the four products (Figure 2.1). Their inclusion is solely to present evidence, which may help explain other obtained data. It is important to note that the reactions for Compound I and Compound IV seem to have went to completion as no starting aldehyde material is present in either. Compound III appears to only have trace amounts, whereas Compound II seemed to contain heavy portions of the beginning aryl aldehyde.

Compound I

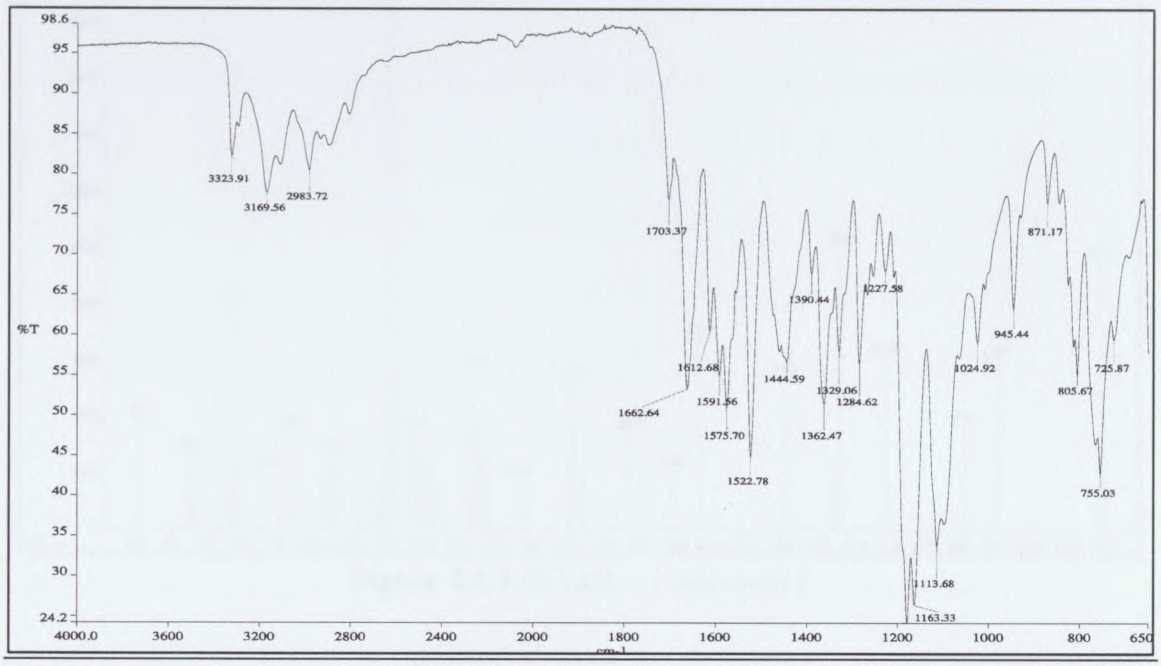


Figure 2.2.1 *IR – Compound I*

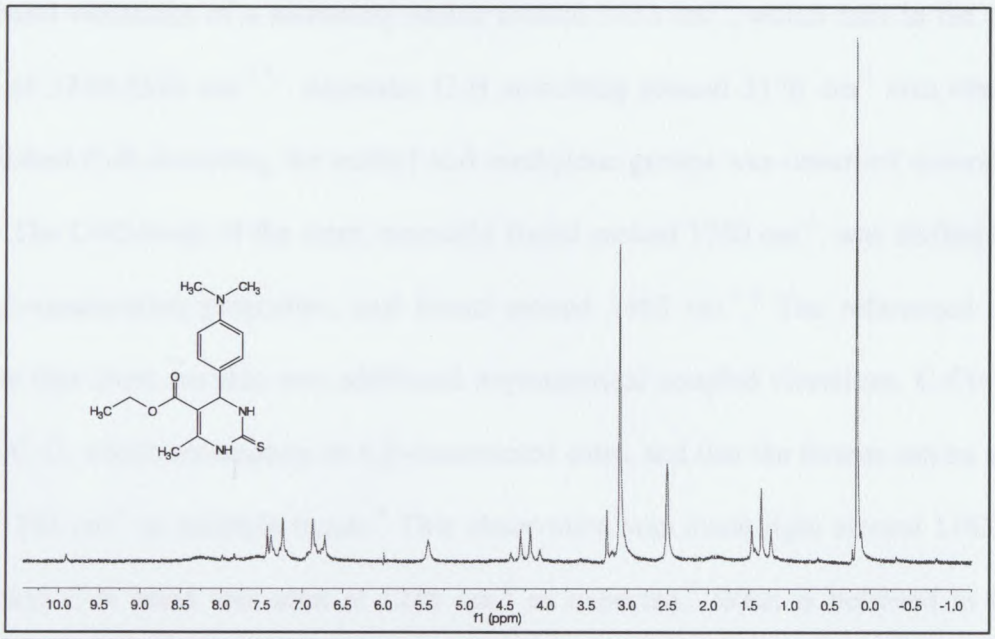


Figure 2.2.2 *^{1}H-NMR – Compound I*

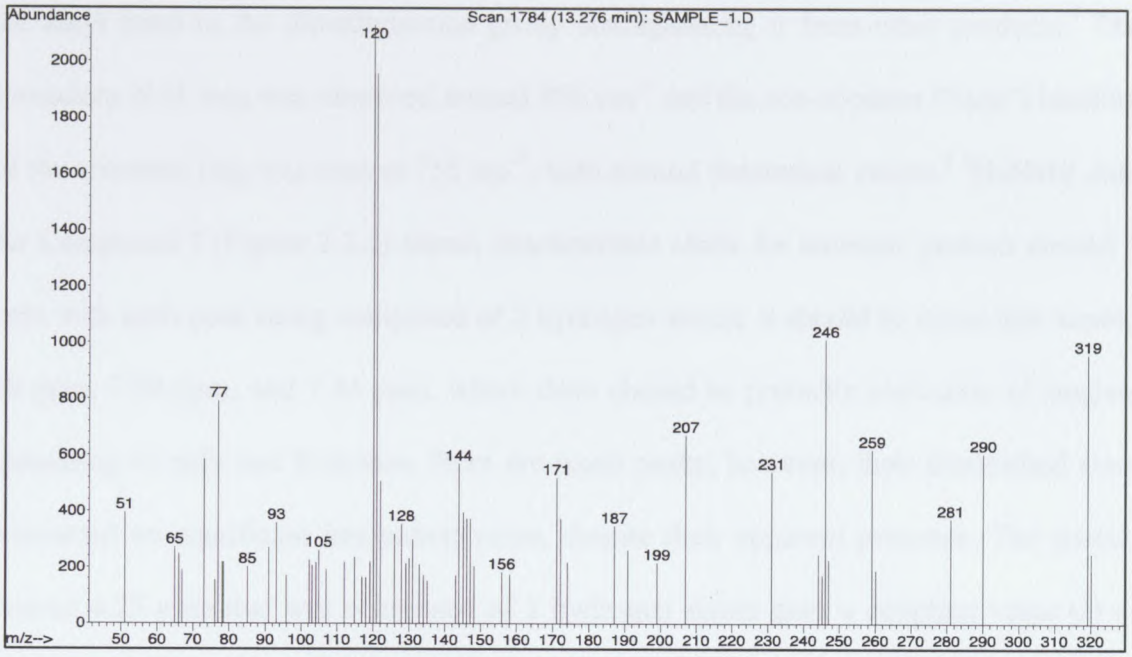


Figure 2.2.3 *GC-MS – Compound I*

Analysis of IR data for compound I (Figure 2.2.1) using published literature[9,10] suggested N-H bond vibrations of a secondary amine around 3323 cm^{-1}, which falls in the typical range of 3350-3310 cm^{-1}.[9] Aromatic C-H stretching around 3170 cm^{-1} was observed. Established C-H stretching for methyl and methylene groups was observed around 2984 cm^{-1}.[9] The C=O bond of the ester, normally found around 1750 cm^{-1}, was shifted due to the α,β-unsaturation properties, and found around 1663 cm^{-1}.[9] The referenced source dictates that there are also two additional asymmetrical coupled vibrations, C-C(=O)-O, and O-C-C, which accompany an α,β-unsaturated ester, and that the former can be seen at 1300-1163 cm^{-1} as multiple bands.[9] This observation was made right around 1163 cm^{-1}. The alkyl C-N bond was seen at 1285 cm^{-1} as expected.[9] What is believed to be the thiocarbonyl group (C=S) was observed around 1285 cm^{-1} as it fell close to the suggested frequency.[9] The observed peak around 945 cm^{-1} was suggestive of the C-C-N bending of

the alkyl bond in the dimethylamino group distinguishing it from other products.[9] The secondary N-H wag was observed around 806 cm^{-1} and the out-of-plane ("oop") bending of the aromatic ring was seen at 755 cm^{-1}, both around theoretical values.[9] ^{1}H-NMR data for Compound I (Figure 2.2.2) shows characteristic shifts for aromatic protons around 7 ppm with each peak being comprised of 2 hydrogen atoms. It should be noted that around 10 ppm, 7.99 ppm, and 7.84 ppm, where there should be probable indication of singlets consisting of only one H-proton, there are small peaks; however, their diminished sizes warranted no significant integration value, despite their apparent presence. The quartet around 4.25 ppm that was comprised of 2 hydrogen atoms gave a coupling value (J) of 7.8 Hz, while the triplet around 1.3 ppm formed from 3 hydrogen atoms also gave a coupling value of J = 7.8 Hz, confirming the adjacent nature of the two sets of protons. This suggested the presence of an ethyl group. At 3.1 ppm the observed singlet consisting of 6 protons was indicative of the two CH_3 groups making up the dimethylamino moiety, while the singlet around 2.5 ppm made up of 3 protons showed the presence of an isolated methyl group. The tall peak around 0.0ppm was identified as the TMS reference peak. Mass spectrum data for Compound I (Figure 2.2.3) confirmed the molecular formula $C_{16}H_{21}O_2N_3S$ with a M^+ peak at 319 m/z.

Compound II

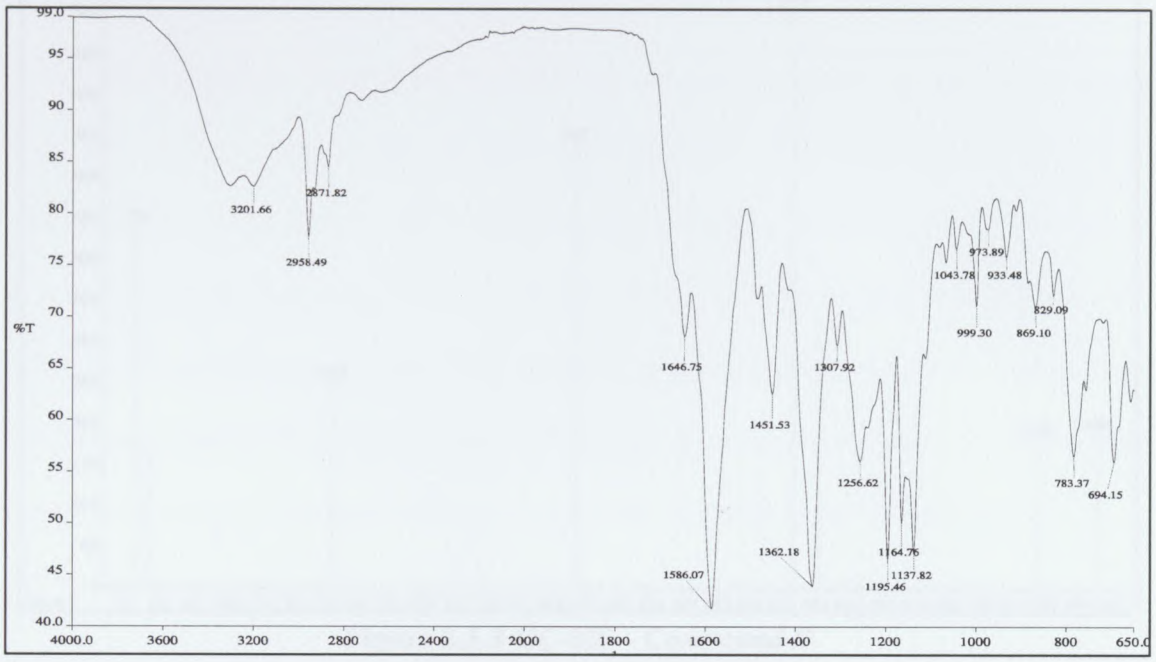


Figure 2.3.1 *IR – Compound II*

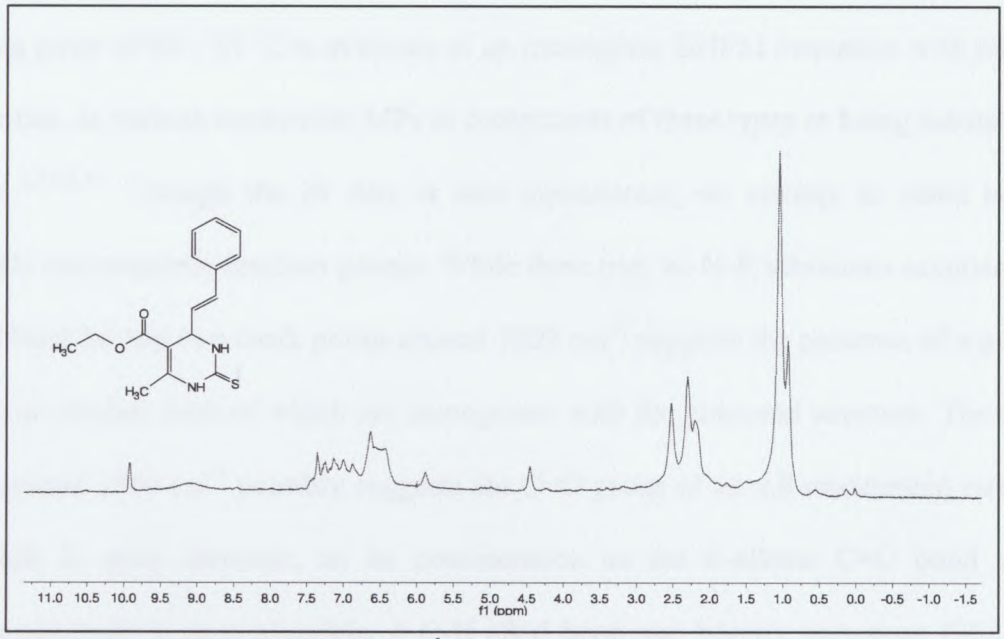


Figure 2.3.2 *^{1}H-NMR – Compound II*

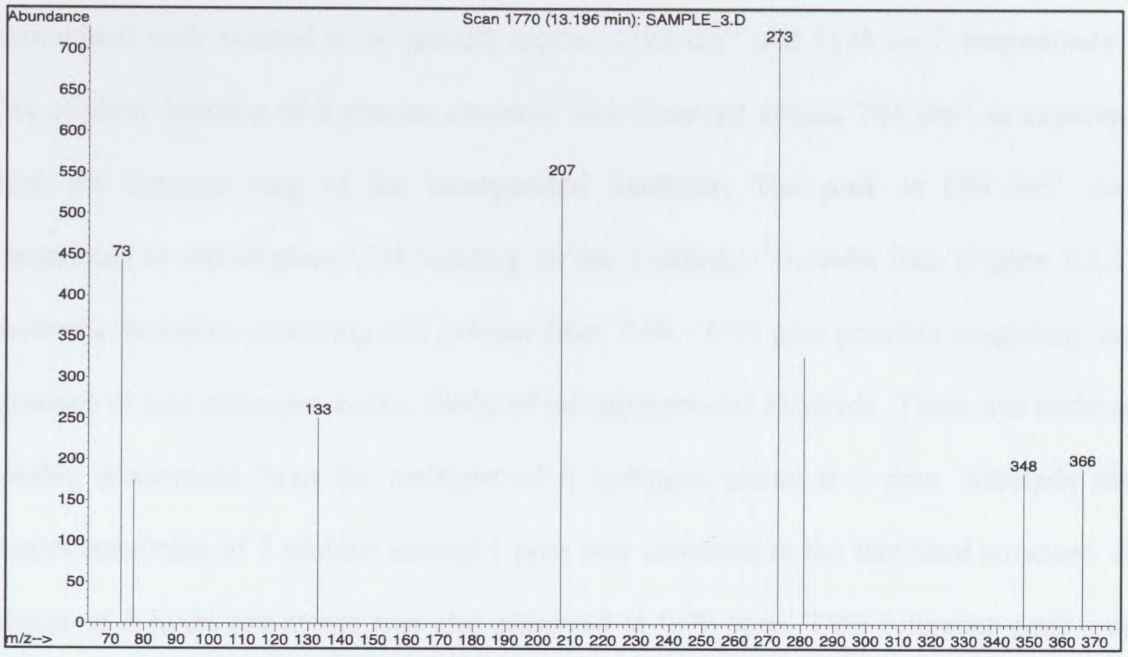


Figure 2.3.3 *GC-MS – Compound II*

As mentioned, formation of Compound II was unsuccessful as indicated by MP (Table 2.1), IR (Figure 2.3.1), ^{1}H-NMR (2.3.2), and GC-MS data (Figure 2.3.3). The recorded melting point of 80 – 83 $^{\circ}$C is evidence of an incomplete DHPM formation with possible impurities, as various works note MPs in compounds of these types as being substantially higher.[2,5,6,8,11] Though the IR data is also inconsistent, we attempt to make note of possible characteristic function groups. While there may be N-H vibrations occurring, the broad band having two weak points around 3202 cm^{-1} suggests the presence of a primary amine or alcohol, both of which are incongruent with the proposed structure. The strong peak around 1586 cm^{-1} possibly suggests the C=O group of an α,β-unsaturated ester, but the shift is quite dramatic, so its consideration as the E-alkene C=C bond of the cinnamaldehyde is most plausible. A C-N alkyl bond was heavily present at 1362 cm^{1}.[9] The peak around 1257 cm^{-1} is a potential representation of a C=S group as per literature.[9]

Despite uncertainty in the C=O group, the two asymmetric peaks associated with the α,β-unsaturated ester seemed to be present around 1195 cm^{-1} and 1138 cm^{-1}, respectively.[9] Out-of-plane bending of a present aromatic was observed around 783 cm^{-1} as expected from the benzene ring of the incorporated aldehyde. The peak at 694 cm^{1-} was contributed to out-of-plane C-H bending on the E-alkene. ^{1}H-NMR data (Figure 2.3.2) showed a multiplet consisting of 5 protons from 7.46 – 6.28 ppm possibly suggesting the presence of aryl hydrogen atoms, likely of the incorporated aldehyde. There was nothing notably discernable from the multiplet of 6 hydrogen atoms at 2 ppm. Similarly the singlet consisting of 5 protons around 1 ppm was unrelated to the theorized structure. A singlet of 3 hydrogen atoms was also observed at 0.90 ppm. TMS reference peak was observed at 0.0 ppm. Mass spectrum data for Compound II (Figure 2.3.3) refuted the theorized molecular formula $C_{16}H_{18}O_2N_2S$ with a M^+ peak at 366 m/z, a difference of 64 m/z. Reasoning for the unsuccessful formation of Compound II will be discussed in the conclusion section.

Compound III

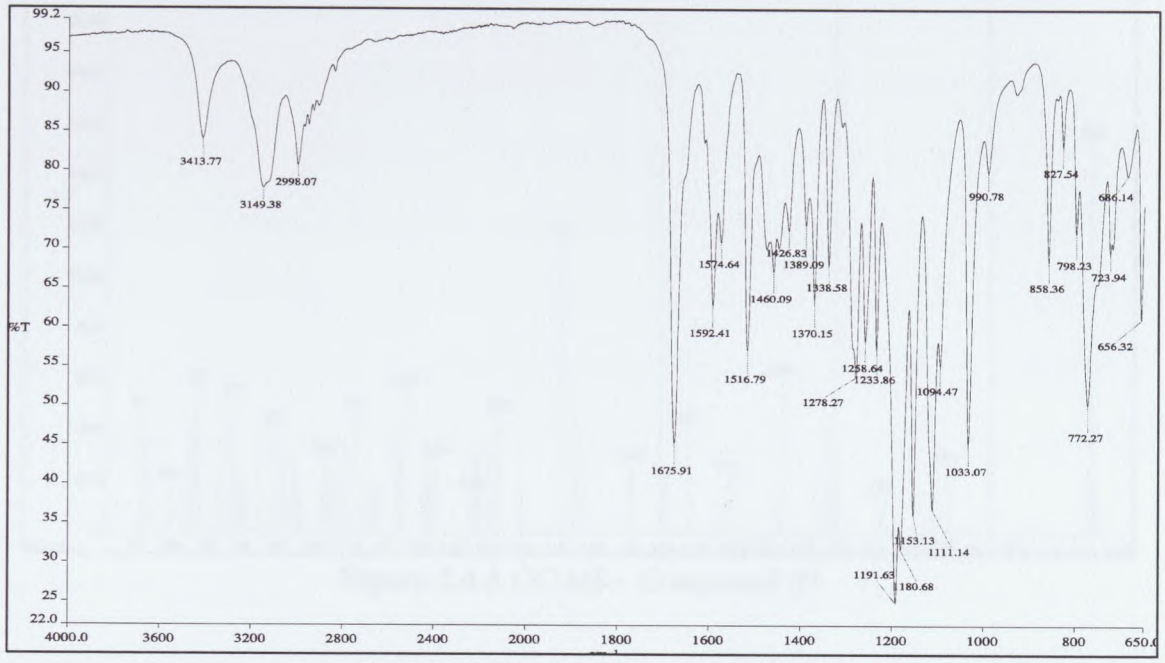


Figure 2.4.1 *IR – Compound III*

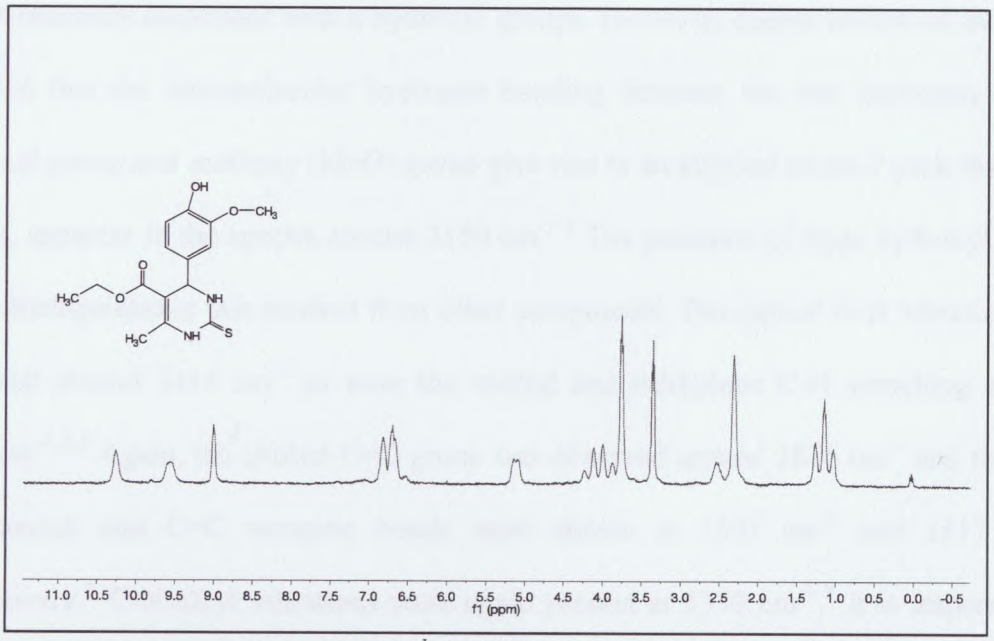


Figure 2.4.2 *^{1}H-NMR – Compound III*

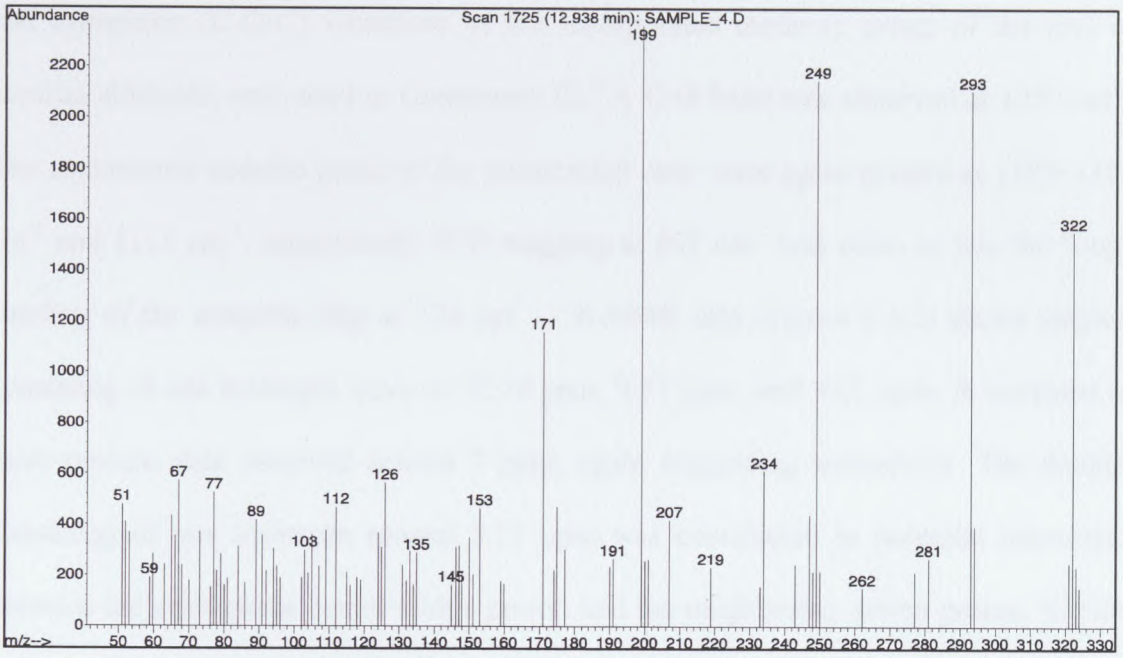


Figure 2.4.3 *GC-MS – Compound III*

Initial study of the IR data for compound III (2.4.1) suggested the absence of the alcohol group, which is expected in the theorized product. Specifically, there was no observable peak commonly associated with a hydroxyl groups. However, deeper review of literature revealed that the intermolecular hydrogen bonding between the free hydrogen of the hydroxyl group and methoxy (MeO) group give rise to an atypical alcohol peak that was, in fact, apparent in the spectra around 3150 cm^{-1}.[9] The presence of these hydroxyl peaks made distinguishable this product from other compounds. The typical N-H vibration was observed around 3414 cm^{-1} as were the methyl and methylene C-H stretching around 2998 cm^{-1}.[8,9] Again, the shifted C=O group was observed around 1676 cm^{-1} and the C-C ring stretch and C=C aromatic bonds were shown at 1592 cm^{-1} and 1517 cm^{-1}, respectively.[9] C-N alkyl vibrations were again present at 1370 cm^{-1}.[9] It is important to point out here two peaks that further distinguish and confirm this compound theorized structure. At 1278 cm^{-1} and 1033 cm^{-1} are peaks representing the asymmetric (C-O-C)

and symmetric (C-O-C) vibrations of the incorporated methoxy group of the aryl o-vanillin aldehyde, only used in Compound III.[9] A C=S band was observed at 1259 cm^{-1}. The asymmetric coupled peaks of the unsaturated ester were again present at 1192–1153 cm^{-1} and 1111 cm^{-1}, respectively. N-H wagging at 858 cm^{-1} was seen, as was the "oop" bending of the aromatic ring at 772 cm^{-1}. ^{1}H-NMR data (Figure 2.4.2) shows singlets consisting of one hydrogen atom at 10.28 ppm, 9.57 ppm, and 9.02 ppm. A multiplet of three protons was observed around 7 ppm, again suggesting aromaticity. The doublet consisting of one hydrogen around 5.13 ppm was contributed to potential interaction between the stereogenic center's lone proton and the neighboring amino proton. Similar to what was observed in Compound I, a quartet of two hydrogen atoms having a J value of 7.8 Hz was seen at 4.08 ppm, as was a triplet of three protons around 1.17 ppm also having a J value equal to 7.8 Hz. This indicated the ethyl group contained in the structure. Two singlets consisting of three hydrogen atoms at 3.71 and 2.32 ppm were demonstrative of the two isolated methyl groups. TMS reference peak was observed at 0.0 ppm. Mass spectrum data for compound III (Figure 2.4.3) confirmed the proposed molecular formula $C_{15}H_{18}N_2O_4S$ with a M^+ peak of 322 m/z.

Compound IV

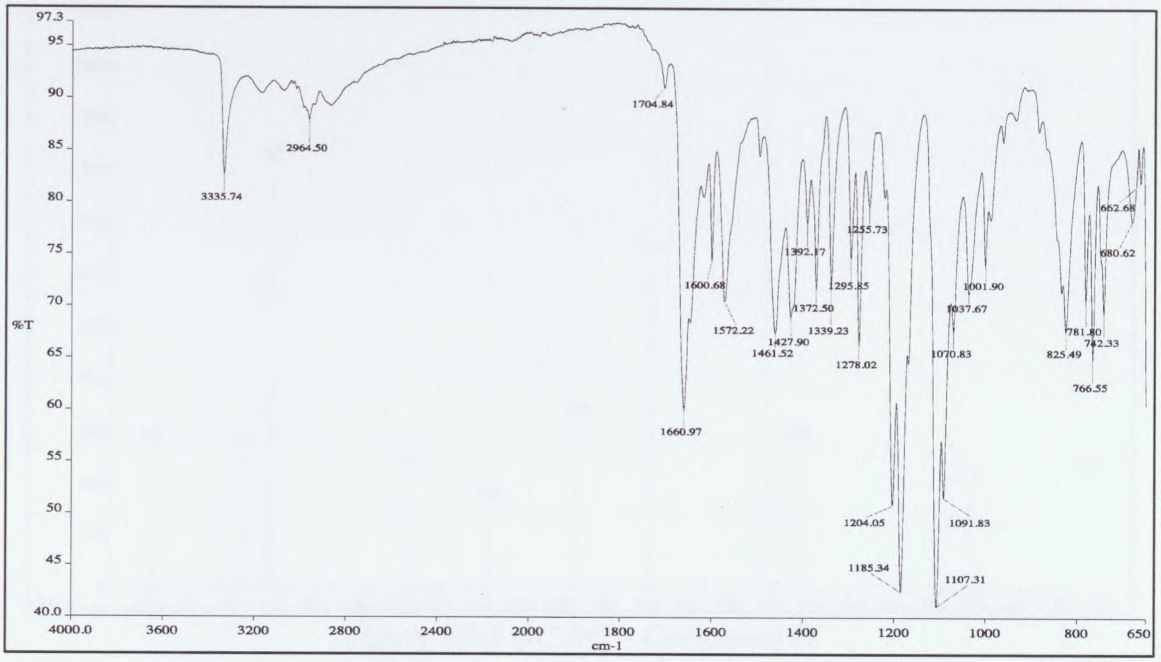


Figure 2.5.1 *IR – Compound IV*

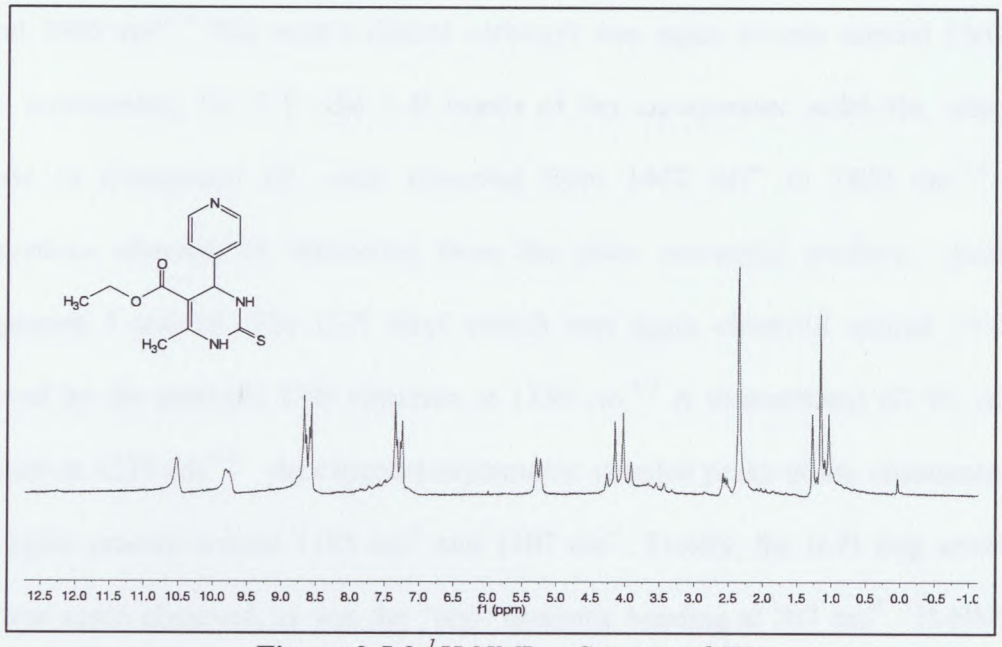


Figure 2.5.2 *^{1}H-NMR – Compound IV*

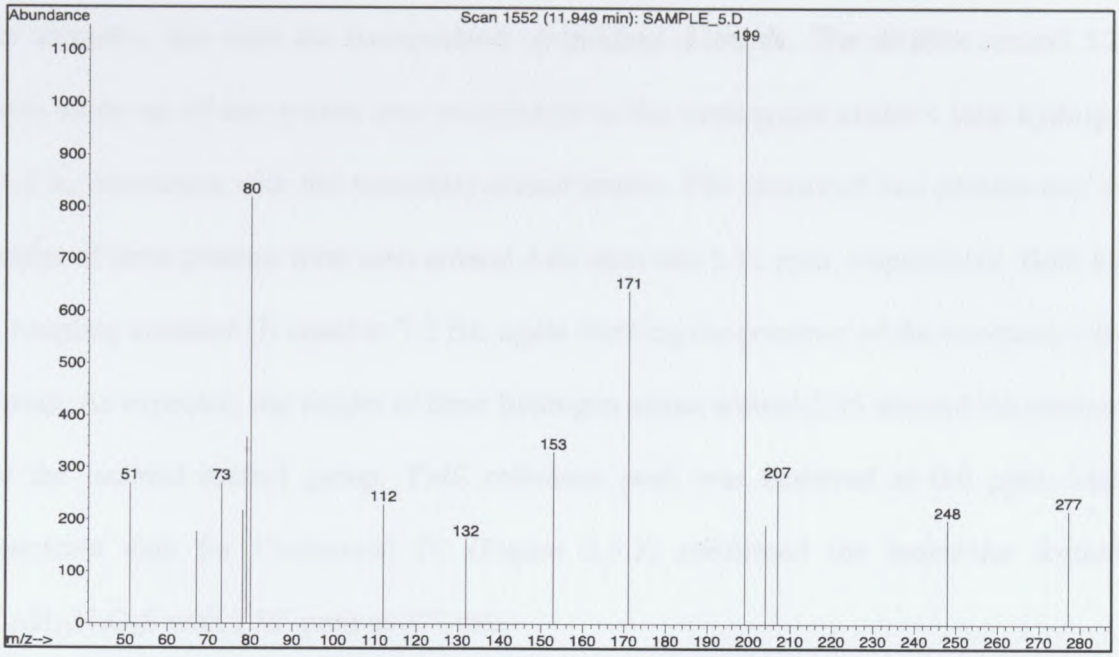


Figure 2.5.3 *GC-MS – Compound IV*

IR data for Compound IV (Figure 2.5.1) shows the same 2° N-H peak around 3336 cm^{-1} that was seen for other successfully formed products, as well as the C-H vibrations around 2965 cm^{-1}.[9] The ester's shifted carbonyl was again present around 1661 cm^{-1}. Peaks representing the C-C and C-N bonds of the incorporated aldehyde, which was specific to Compound IV, were observed from 1462 cm^{-1} to 1428 cm^{-1}.[9] These observations allowed for distinction from the other successful products, specifically Compounds I and III. The C-N alkyl stretch was again observed around 1373 cm^{-1} followed by the aromatic C-N vibration at 1339 cm^{-1}.[9] A thiocarbonyl (C=S) vibration was seen at 1278 cm^{-1}.[9] As expected asymmetric coupled peaks of the unsaturated ester were again present around 1185 cm^{-1} and 1107 cm^{-1}. Finally, the N-H wag around 825 cm^{-1} was again observed, as was the "oop" aromatic bending at 767 cm^{-1}. ^{1}H-NMR data (Figure 2.5.2) shows singlets having one hydrogen atom around 10.52 ppm and 9.79

ppm. At 8.62 ppm and 7.26 ppm multiplets made of two protons were indicative again of an aromatic, this time the incorporated pyrimidine aldehyde. The doublet around 5.25 ppm made up of one proton was contributed to the stereogenic center's lone hydrogen and its interaction with the secondary amino proton. The quartet of two protons and the triplet of three protons were seen around 4.08 ppm and 1.15 ppm, respectively. Both had a coupling constant (J) equal to 7.2 Hz, again showing the presence of the structures ethyl group. As expected, the singlet of three hydrogen atoms around 2.35 showed the presence of the isolated methyl group. TMS reference peak was observed at 0.0 ppm. Mass spectrum data for Compound IV (Figure 2.5.3) confirmed the molecular formula $C_{13}H_{15}N_3O_2S$ with a M^+ peak at 277 m/z.

Conclusion

We attempted to synthesize four dihydropyrimidinone thione analogs differing solely about the aryl aldehyde moiety. The syntheses of DHPMs were achieved through one-pot, three-component, Biginelli Condensation Reactions under solvent-free conditions using zinc chloride ($ZnCl_2$) as the catalyst. We found that three products, Compound I, Compound III, and Compound IV, successfully formed, and that Compound II did not. IR, NMR, and GC-MS analyses were carried out to study and confirm the properties of those products successfully synthesized. Further confirmation in theses findings was gained through comparing our analysis data to other works involving compounds of generally similar characterization.[2,6,8,11]

Based on the aryl aldehydes, which were used in the successful products of our study and the aldehyde used in the failed formation of Compound II, we theorize that the reagent, which will become the substituent at the C-4 position of the DHPM, must initially

embody certain properties for one to obtain desired compounds. Specifically, we propose that directly alpha to the O=C-H group there must be aromaticity rather than an aliphatic group like that seen in compound II's aldehyde, as this leads to poor yields and side products. Other studies also note this same compromise in using aliphatic aldehydes, and our findings seem to confirm those assertions.[1,8] In summary, we have found that the use of $ZnCl_2$ in the Biginelli reaction is a viable means for obtaining our desired products with the exception of compound II, and that the conditions described in our synthetic routes are facile, safe, and conducive to our respective products' formation.

Future of Dihydropyrimidinones

As mentioned early on in the report, the remarkable biological activity of dihydropyrimidinones and their thione analogs has been, and continues to be, the driving force behind the surge of spanning research efforts made by many different scientists. However, two significant challenges persist: First, finding the perfect functionalization for the DHPM derivatives that will allow these compounds to execute their intended jobs with minimal side effects, whether it is treating autoimmune symptoms, alleviating hypertension, or even destroying oncological diseases. Second, finding a facile synthetic route for DHPM production that is not only efficient, but also environmentally sound. While these issues remain a prominent association for these compounds and their respective reactions, we predict that the promise that lies in their potential applications will generate the drive of biologist and chemist alike to both overcome said challenges and continue discovering remediation for the current diseases that wreak havoc in our world.

REFERENCES:

(1) Singh, K.; Singh, K. *Adv. Heterocycl. Chem.* **2012**, *105*, 224-225, 259.

(2) D. L. da Silva et al. *Bioorg. Med. Chem.* **2012**, *20*, 2645-2650.

(3) Naseem, A.; van Lier, J. E. *Tetrahedron Lett.* **2007**, *48*, 5407-5409.

(4) Bhavya, K.; Purohit, M. N.; Pujar, G. V. *Indian Drugs.* **2011**, *48*, 7-14.

(5) Qingjian, L.; Ning, P.; Jiehua, X.; Wenwen, Z.; Fanpeng, K. *Synth. Commun.* **2013**, *43*, 139-146.

(6) Dadhania, A. N.; Patel, V. K.; Raval, D. K. *J. Chem. Sci.* **2012**, *124*, 921-926.

(7) Srivastava, V. *Green Sustainable Chem.* **2013**, *3*, 38-40.

(8) Debache, A.; Chouguiat, L.; Boulcina, R.; Carboni, B. *Open Org. Chem. J.* **2012**, *6*, 12-20.

(9) Klein, D. *Organic Chemistry.* Hoboken: John Wiley & Sons, Inc. 2012. Print.

(10) Silverstein, R. M. et al. *Spectrometric Identification of Organic Compounds.* Hoboken: John Wiley & Sons, Inc. 2015. Print.

(11) Chand, S.; Sandhu, S.; Sandhu J. S.; *J. Chem.* **2012**, *5*, 194-198.