ONE-POT MULTICOMPONENT COUPLING SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-PYRAN DERIVATIVES USING DEEP EUTECTIC SOLVENTS (DES)

By

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I dedicate this work to the soul of my father, who passed away while I am far away busy with this work. He taught me that education empowers individuals to make a positive changes within their communities.

ACKNOWLEDGMENTS

This work would not be possible without the support of many great people around me. I extend my sincere thanks to my brother, **Mazen**, for his endless support and encouragement. Without his support, I would not be able to achieve this dream. Thank you Mazen.

I would like to thank my advisor, Dr. Scott Handy, for his encouragement and enthusiasm that were invaluable to the success of this work. I would also like to thank Dr. Paul Kline and Dr. Kevin Bicker for serving on my committee. Also, I would like to thank the faculty and staff in the Department of Chemistry at Middle Tennessee State University (MTSU) for their help and support.

Lastly, I would like to thank my family for their loving, support and understanding over the past three years, while I spent great deal of time away from them to complete this work. I am thankful for my loving wife, **Areej Alsubhi**, as well as for my mother, siblings, and my son and daughter, Meshary and Lara. Thank you Areej, for your support and understanding.

ABSTRACT

Considering the importance of 2-Amino-3-cyano-4*H*-pyran derivatives and the need for the development of new environmental friendly synthetic methodologies, the combination of Multicomponent Coupling reactions (MCR) and Deep Eutectic solvents (DES) was the goal of our study in order to make the reaction more environmentally, as well as economically, viable. Moreover, a simple work up procedure was developed via recrystallization from ethanol or ethanol-water to avoid the use of expensive silica gel chromatography and exclude the massive use of organic chromatography eluents. Finally, this work avoids the use of toxic and expensive catalyst or solvents.

Interestingly, increasing the reaction scale from 1 mmol to 3 mmol improved the reaction isolated yield. A variety of substituted aromatic as well as heteroaromatic aldehydes were explored using the larger 3 mmol scale. Generally, electron withdrawing groups (EWG) on the aldehyde produced lower yields comparing with the electron donating groups (EDG). Lastly, an evaluation of the sequence addition off the reaction components was performed. The study shows that by mixing benzaldehyde, malononitrile, and adding dimedone after five minutes, in accordance with the Mantelingu procedure, the yield increases dramatically and the side reactions are limited.

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CHAPTER I

INTRODUCTION

While there are many interesting structural families that have been reported and targeted over the years, polyfunctionalized 2-amino-3-cyano-*4H*-pyran derivatives certainly have occupied a place as an important class of heterocyclic organic compounds due to their biological and pharmacological behavior (Figure 1). [1-5] This class of compounds are used as anticancer,[1] spasmolytics, anti-anaphylactics, cytotoxic, anti-HIV, anti-inflammatory, antimalarial, antimicrobial,[2] antihyperglycemic, antidyslipidemic, and for Alzheimer treatment. [5] The following sections summarize some of these biological applications and will set the stage for the synthetic studies that will be discussed later.

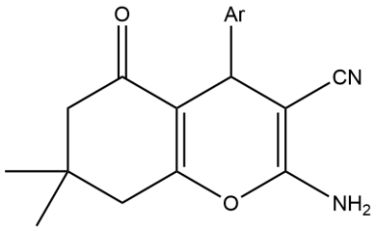


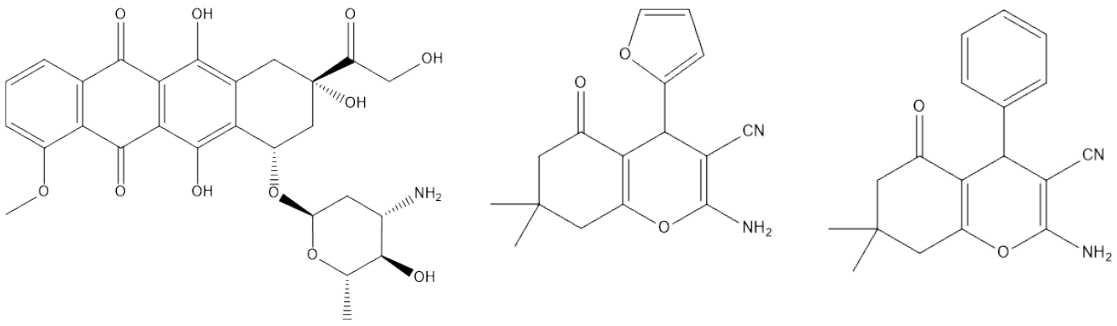
Figure 1: General structure for 2-amino-4*H*-chromene-3-carbonitrile derivatives.

Biological activities

Antitumor activities

Al-Omran *et al.* studied the effects of the two synthesized products **1** and **2** (Figure 2) on the *in vitro* growth of human tumor cell lines. [1] Three human tumor cell lines and three normal cell lines were selected. The effectiveness of **1** and **2** were evaluated after exposing three human tumor cell lines and three normal cell lines to

different concentrations of **1** or **2** and comparing this result with the result of exposing three human tumor cell lines to doxorubicin (Figure 2).



Doxorubicin **1** **2**

Figure 2: Illustration of the structure of the pyran compounds **1** and **2** and doxorubicin.

Both **1** and **2** were able to inhibit growth of the human tumor cell lines. Compound **1** shows very interesting inhibitory effects toward the three tumor cell lines. The IC_{50} value of compound **1** showed that it has higher inhibitory effect towards the three cancer cell lines. On the other hand, both compounds inhibit the growth of normal cell lines, more than doxorubicin.

Antibacterial activities

Kumar and co-worker reported the antibacterial activity of 2-amino-4*H*-chromene-3-carbonitrile derivatives as determined by screening against three bacterial strains.[2] The bacterial strains used were *Escherichia coli* (MTCC 41), *Staphylococcus aureus* (MTCC 1144) and *Pseudomonasputida* (MTCC 1072) (Figure 3).

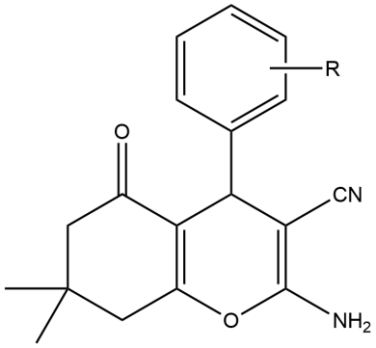


Figure 3: General structure of compounds used by Kumar and co-worker.

In general, compounds in which R is p-methoxy, m-nitro, p-nitro, p-chloro and m-hydroxy showed complete inhibition at 128 mg/mL or less, while compounds in which R is H or methyl showed incomplete inhibition. Specifically, the p-nitro containing compound shows a notable overall potency, while the p-methoxy and m-hydroxy containing compounds showed selective inhibition towards *Escherichia coli* and *Pseudomonasputida* respectively.

Antitubercular activities

In their study, Kamdar *et al.* assessed the biological activities of the three groups of compounds represented in (Figure 4).[3] The most interesting results came from the antitubercular screening. In this test, they used *Mycobacterium tuberculosis H37Rv* strain and the results were compared with that of the standard drug Rifampicin. Among the three groups of compounds, group 1 (the group of compounds represented in this study) shows the best inhibition strength against tubercular stain. Particularly, the compounds possessing the following substitutions showed the greatest inhibition (72-92 %): p-fluoro, p-hydroxy, m-chloro and m-methoxy.

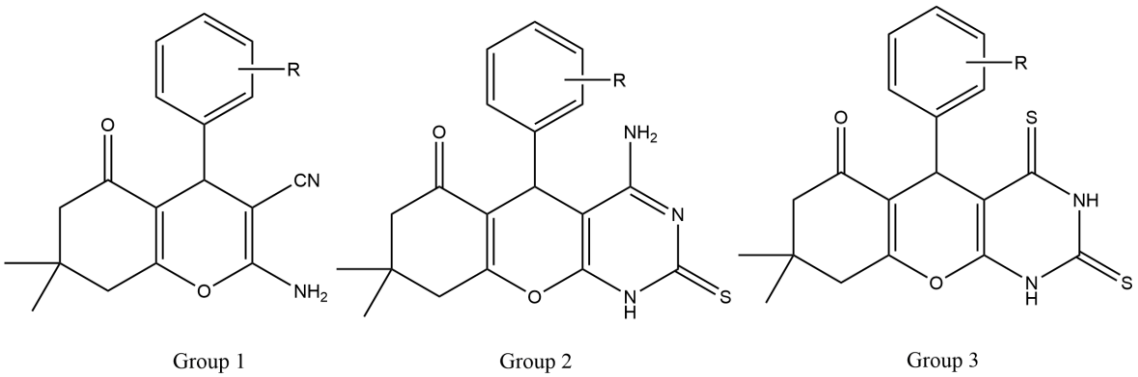


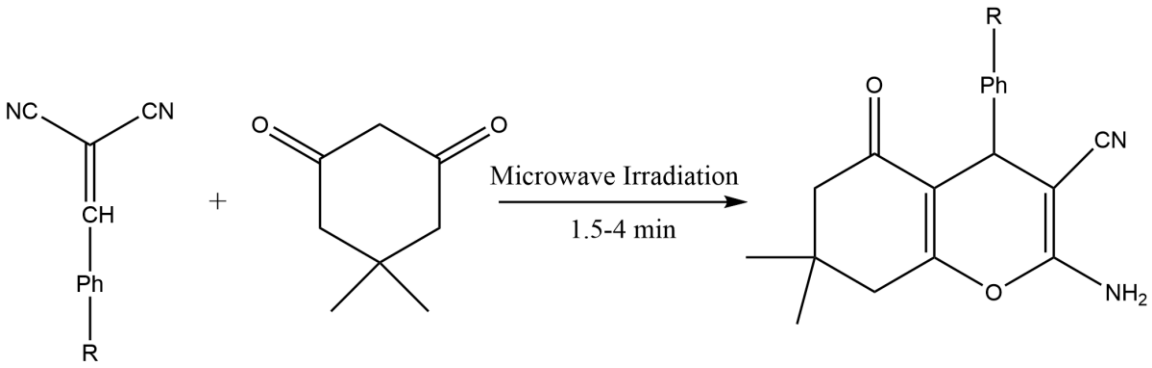
Figure 4: Kamdar *et al.* studied the antitubercular activities of these three groups.[3]

Treatment of neurodegenerative diseases

Neurodegenerative diseases include, but are not limited to, Alzheimer, Parkinson, Schizophrenia and Amyotrophic Lateral Sclerosis (ALS). AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors usually contribute to the processes of synaptic plasticity, which affect learning, memory, excitotoxicity, and neuroprotection.[4] Modifications in AMPA receptors at the postsynaptic membrane affect the synaptic plasticity strength.[5] The direct modulating of AMPA receptors proved to have a positive effect on neurodegenerative conditions, but raises the risk of a condition referred to as "overstimulation." On the other hand, indirect modulation of the AMPA receptor has been raised as another approach to treat neurodegenerative diseases by enhancing neuroplasticity. 2-Amino-3-cyano-*4H*-pyran derivatives proved to be positive modulators of AMPA receptors.

Synthesis of 4*H*-chromenes

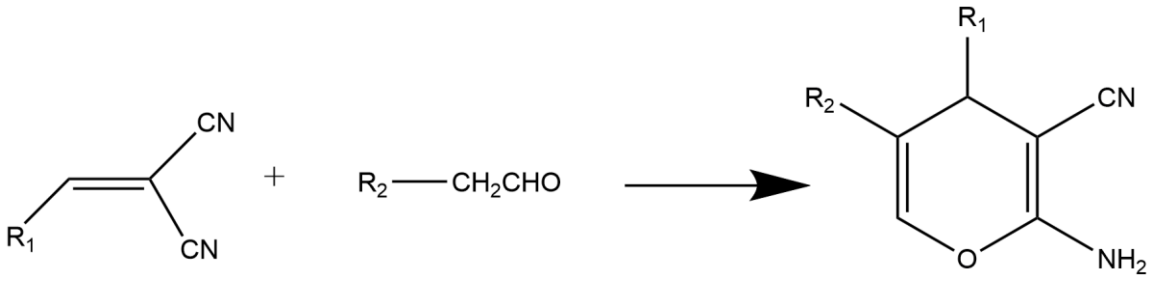
Based upon such a wide spectrum of applications, this class of heterocyclic compounds has drawn synthetic chemists' interest to develop more efficient synthetic routes. Thus, there have been many reported methods to synthesize these compounds.[4-10] A common way to synthesize these compounds is via the reaction between arylidenemalononitriles and activated methylene compounds either under thermal conditions, with the aid of organic bases,[6,7] or under microwave irradiation (Scheme 1).[8] Since the arylidenemalononitriles themselves have to be synthesized in a separate step from aldehydes and malononitrile, an obvious disadvantage of this approach is that it requires at least two separate reactions and thus two separate isolation/purification sequences.



Scheme 1: Synthesis of 2-Amino-3-cyano-4*H*-pyran derivatives under microwave irradiation.[8]

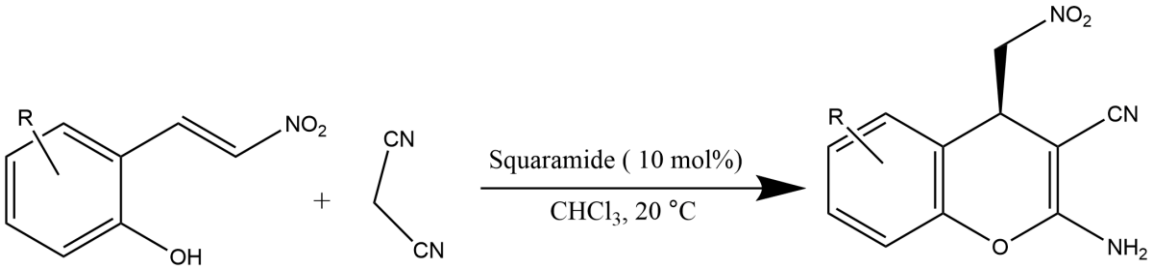
One of the traditional ways to prepare 2-amino-4*H*-chromene-3-carbonitrile derivatives uses arylidenemalononitriles and a nucleophile as starting material (Scheme

2). There have been a good number of old and recent publications that used this approach. For instance, Quintela *et al.* reported a method where they added ethyl acetoacetate to arylidenemalononitriles under reflux conditions.[9] Starting from arylidenemalononitriles requires a previous step for its preparation, which means more labor and purification steps, and makes this approach more costly for large scale application. Thus, the importance of these compounds in both pharmaceutical and industrial application required a new approach that use cheap and readily available starting materials.



Scheme 2: General scheme for the reaction of arylidenemalononitriles with nucleophile.

Another approach was reported by Z. Zhou *et al.* using 2-(*E*)-2-nitrovinylphenol and malononitrile as starting materials (Scheme 3).[10] They used different chiral bifunctional squaramides as an organocatalyst. Following their work, Du and Gao were able to use a similar approach to synthesize these products with high enantioselectivity.[11] In their study, they provided a single example of an asymmetric nucleophile, which raises questions regarding the generality of this method.



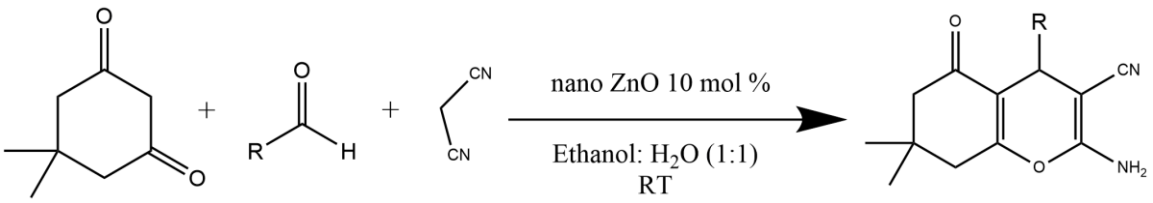
Scheme 3: Michael addition and intramolecular cyclization by reacting using 2-(*E*)-2-nitrovinylphenol with malononitrile.

Multicomponent coupling reactions (MCRs)

The rapid discovery of new biological targets has increased the demand on synthetic chemists to introduce new synthetic methods capable of providing easy access to a library of compounds. One way to serve this purpose has been the development of new Multicomponent coupling reactions (MCRs), one of the most useful synthetic methodologies to produce compound libraries.[12,9] MCRs are defined as those reactions in which three or more compounds react together in one pot to form a new product.[9] MCRs give the opportunity for reaching diversity via families of different reactants, and not being limited to bifunctional reactants. MCRs also allow for easy access to a library of important and structurally complex molecules in a one pot fashion by simply varying the starting materials. With MCRs, reaction time and labor effort, such as purification and isolation of intermediates, are minimized. In contrast, to get the same structure in a linear synthesis fashion, multiple steps with multiple workup and/or purification processes are required. In addition, a linear synthesis may produce considerable amounts of

environmentally hazardous wastes after each step in different ways: as reaction media, catalyst waste, and work up solvents.[12]

More related to the work reported in this thesis, Das *et al.* reported a synthesis of of 2-amino-4*H*-chromene-3-carbonitrile derivatives following an MCR approach. [13] The reaction was catalyzed by ZnO nanoparticles in 1:1 ethanol/water media (Scheme 4). They found that the yield was increased by increasing the catalyst load, until they reached 10% mol. At this point, no change was observed up to 25% mol, and beyond that point the yield dropped significantly.



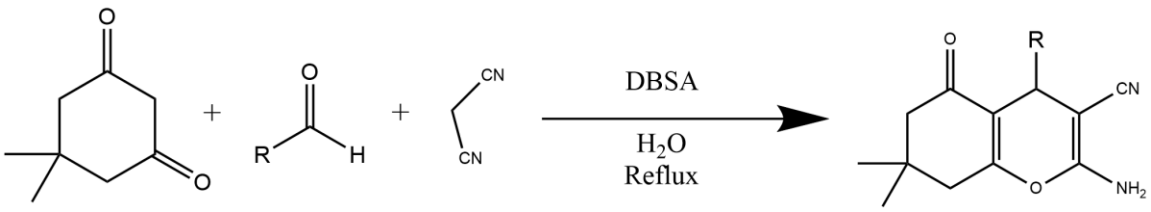
Scheme 4: Three component reaction for the synthesis of of 2-amino-4*H*-chromene-3-carbonitrile derivatives by Das.

Table 1: Summary of Das *et al.* work showing: R substrates, reaction time and the yield.

R	Time (h)	Yield
Ph	3.5	86
4-NO2-C6H4-	3	91
3-NO2-C6H4-	3.5	88
4-F-C6H4-	3.0	90
4-OCH3-C6H4-	4.0	81
4-CH3-C6H4-	3.5	83
4-N(CH3)2-C6H4-	4.0	79
2-Furan	3.0	84
4-Pyran	4.0	81

Above all, the Das method uses a readily available starting material, and follows MCR strategies, which would save considerable time and effort. In addition, the reaction time reported is short and the yield is excellent. However, the preparation and the cost of the ZnO nanoparticles catalyst can be considered as a significant limitation.

Sheikhhosseini *et al.* reported a three-component condensation synthesis of 2-amino-4H-chromene-3-carbonitrile derivatives, in a green media (Scheme 5).[14] They have used p-dodecylbenzenesulfonic acid (DBSA) (Figure 5) as surfactant and catalyst in water. The reaction conditions are mild, but the yield and catalyst amount required is not practical. For example, a 10 mol% loading of DBSA affords a 35% yield after 10 hours at reflux. They had to increase the loading of catalyst up to 25 mol% to achieve high yield. The cost and acidity of DBSA make it impractical for large scale production.



Scheme 5: Reaction using DBSA in aqueous media.

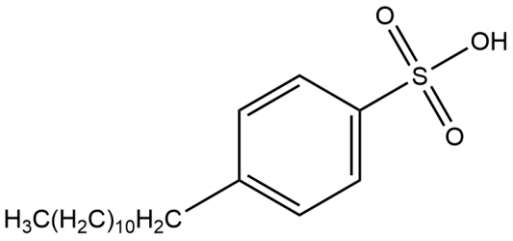
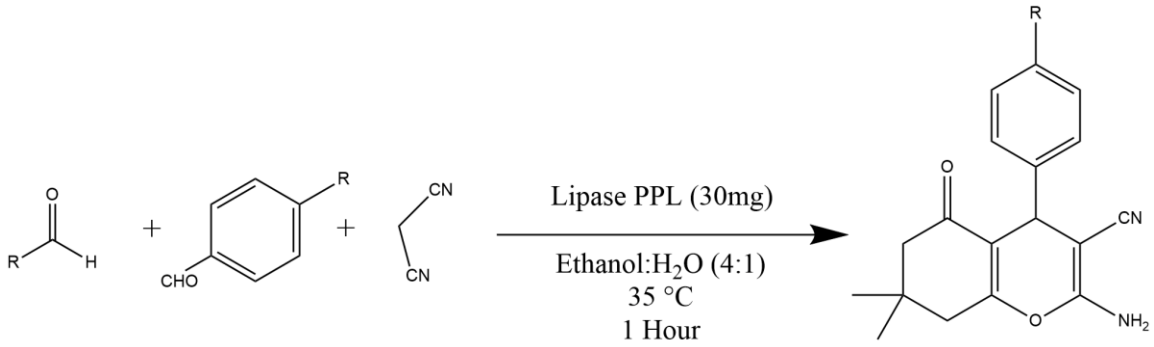


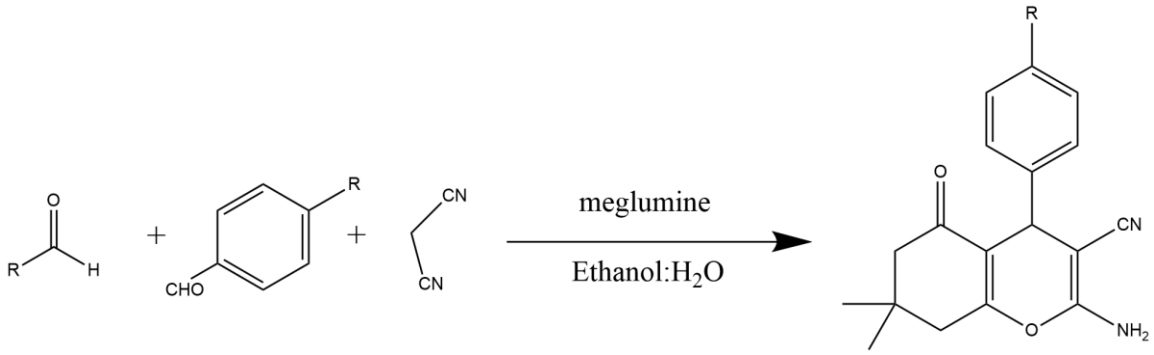
Figure 5: p-dodecylbenzenesulfonic acid (DBSA).

Using Lipase from *Porcine pancreas* (PPL), Zhang *et al.* reported the synthesis of 2-amino-4*H*-chromene-3-carbonitrile derivatives (Scheme 6). [15] The advantages of their work were not only limited to the use of the environmental friendly media, but also extended to the shorter reaction time and the excellent yield. Interestingly, they have studied the effect of the water upon the reaction. The best yield was with ethanol and water 4:1, and the yield dropped sharply with increasing the percent of water.



Scheme 6: Reaction using PPL.

Later in 2013, Zhang employed Meglumine, which is a biodegradable catalyst (Scheme 7). [16] Meglumine is sorbitol derivative that is biodegradable and physiological inert, which makes it suitable for pharmaceutical applications (Figure 6).



Scheme 7: Reaction Using Meglumine as organic catalyst.

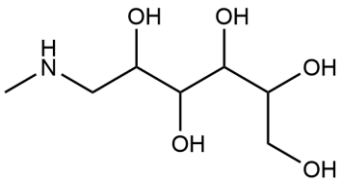
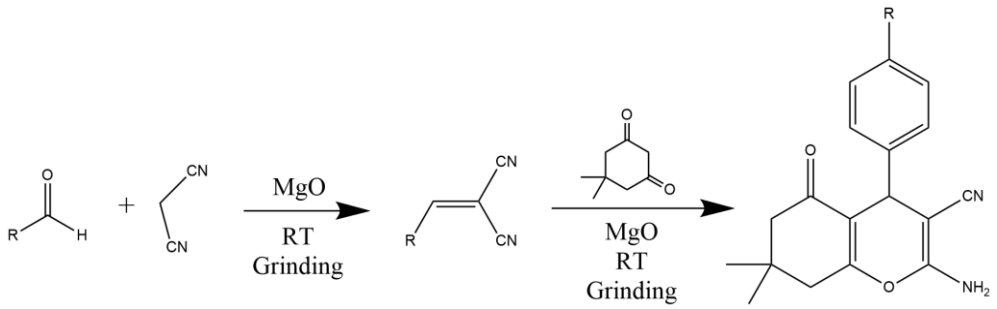


Figure 6: Meglumine.

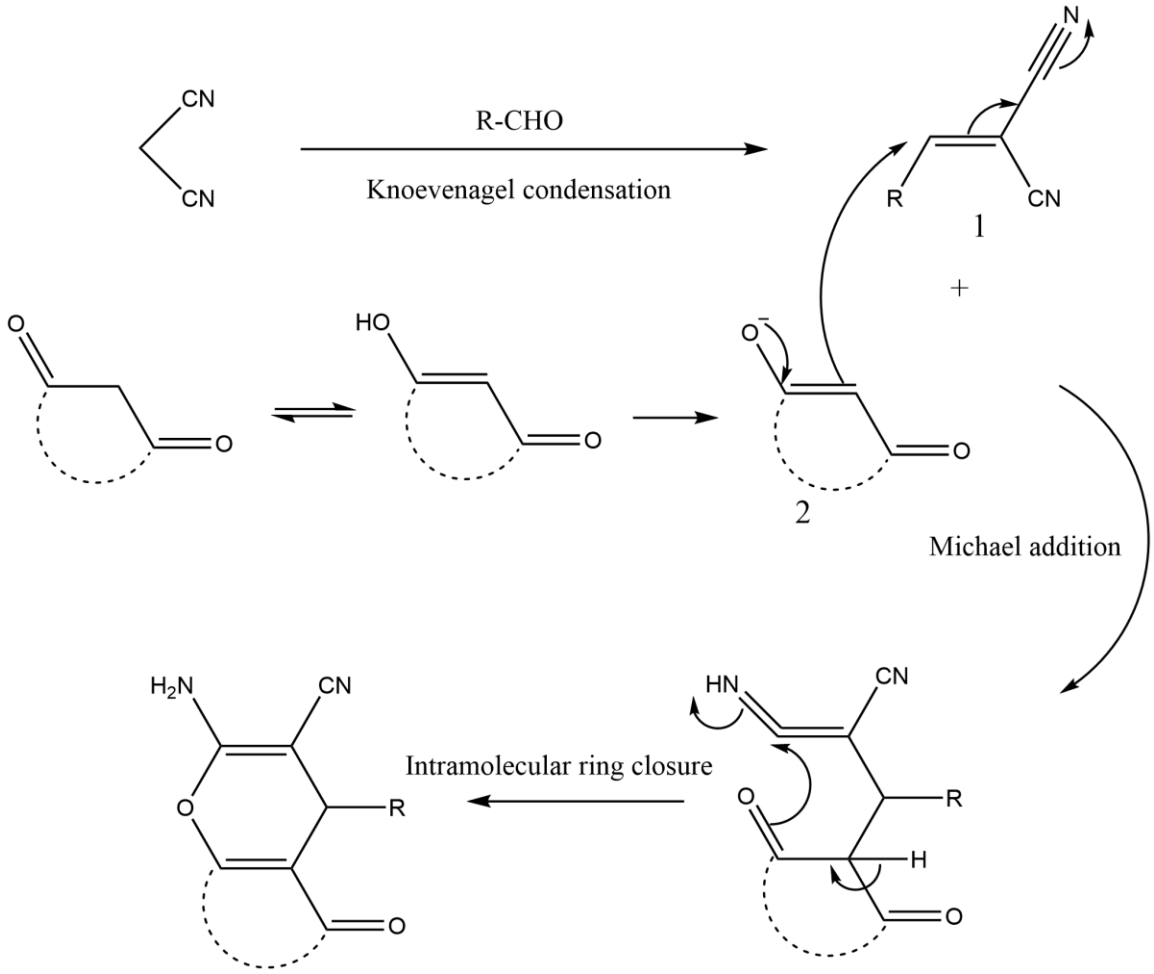
In 2009, Kumar and co-worker reported a two-step, one-pot, solvent-free approach to synthesis of 2-amino-4*H*-chromene-3-carbonitrile derivatives (Scheme 8).[2] Aldehyde, malononitrile and MgO were ground at room temperature for 10 min. Then 5,5-dimethyl-cyclohexane-1,3-dione (dimedone) and 3 drops of water were added to the mixture with continued grinding for another 15 min. The drawback of their work would be in the use of metal oxide and the vigorous mechanical mixing.



Scheme 8: Kumar two steps, one pot synthesis.

Mechanism of the three component coupling of 4H-pyran

The mechanism of the formation of 4*H*-pyran via a three-component coupling strategy is generally accepted to begin with a Knoevenagel condensation between the active methylene compound and the aldehyde, followed by Michael addition with the less reactive active methylene compound, and finally an intramolecular ring closure (Scheme 9).[7,2,11]



Scheme 9: Mechanism of the three component coupling.

This mechanism is highly probable in the case of the traditional approach for synthesizing those compounds where malononitrile and aldehyde are combined first to form arylidenemalononitriles, followed by the addition of the nucleophile, but less clear for simultaneous addition. In addition, a reduction in yields have been observed in this study when combining the three components simultaneous in comparison with combining the malononirtile and aldehyde, then adding the nucleophile after five minutes. With two active methylene compounds present along with the aldehyde, the initial condensation

reaction could occur first with malononitrile or dimedone, each would afford different intermediate. Malononitrile is the more reactive active methylene compound and thus the arylidenemalononitriles intermediate should dominate. With these intermediates formed, condensations can then result in at least 4 products. However, the reactions reported by Azizi and co-workers could be the major route that is competing with the desired reaction.[17] According to their work, two equivalent of dimedone can react with aromatic aldehyde at room temperature or at 90°C to produce excellent yield in short reaction time. This evidence explains the reduction on yields occur when mixing the three component simultaneous.

Deep eutectic solvents (DESs)

Deep eutectic solvents (DESs) are an emerging class of solvents that are considered as ionic liquid analogues.[18] They show ability to dissolve a wide range of solutes, including inorganic salts and metal oxides, due to their ionic nature and polarity.[18-20] They are moisture and chemically stable with suitable physical properties such low vapor pressure and high boiling point.[19] These advantages make DESs good reaction media and favor them over ionic liquids in large scale application. In addition, the ease of preparation, recyclability, biodegradability, and the relatively low cost of its components, make DESs a suitable choice for green chemistry applications.

The first reported work on DESs was on 2001 by Abbott *et al.*[18] In this work, they were trying to introduce a new class of Ionic Liquids (IL) that are less expensive and moisture stable. The initial choices were the combination of imidazolium halides and aluminum trichloride to form chloroaluminates. The main drawback of chloroaluminates

is their moisture sensitivity, even though both the imidazolium and chloroaluminate components are relatively expensive. These two disadvantages would limit the large scale applications of these solvents and made it necessary to investigate other choices to produce cheaper and moisture stable media. Abbot *et al.* used metal chlorides and quaternary ammonium salts instead of the imidazolium-based IL. Among the investigated ammonium salts, they found that choline chloride (ChCl, 2-hydroxyethyl-trimethylammonium chloride) gave the lowest melting points among the other quaternary ammoniums (Figure 7). Thus, choline chloride was the focus in their following work in 2004, where they introduced the term DES for the first time to distinguish between the DESs and traditional ILs.[20]

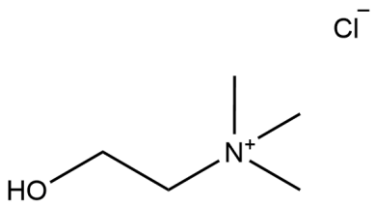
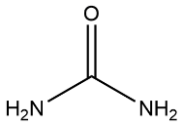


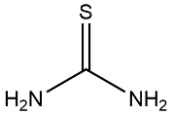
Figure 7: Choline chloride (ChCl, 2-hydroxyethyl-trimethylammonium chloride)

DES is a eutectic mixture of a Lewis or Bronsted acid and a base. In contrast to ILs, DESs are non-reactive with water and biodegradable. They can be formed by mixing a quaternary ammonium salt with a hydrogen bond donor or a metal salt. The hydrogen donor plays a major role in the physical properties of the liquid, hence, it can be manipulated to target a specific application. A wide range of hydrogen bond donors have been employed to form deep eutectic solvents, which possess groups like amides,

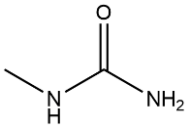
sulfonates, carboxylic acids, and alcohols (Figure 8). Also, a number of inexpensive and safe quaternary ammonium salts have been used (Figure 9).



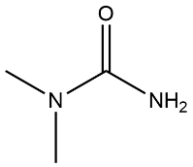
Urea



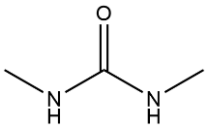
Thiourea



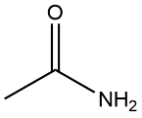
1-methyl urea



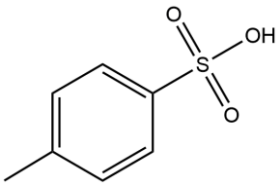
1,1-dimethyl urea



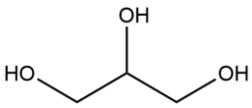
1,3-dimethyl urea



Acetamide

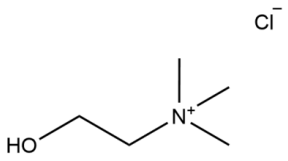


p-Toluenesulfonic acid

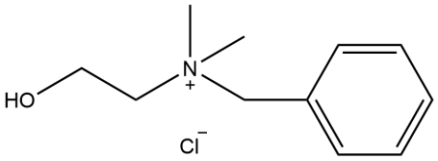


Glycerol

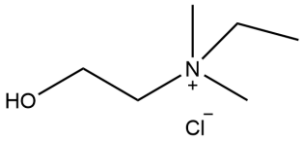
Figure 8: Structures of common hydrogen bond donors used in DES.



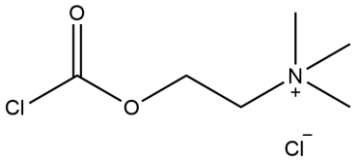
Choline chloride



N-benzyl-2-hydroxy-N,N-dimethylethanaminium chloeide



N-ethyl-2-hydroxy-N,N-dimethylethanaminium chloride



2-(chlorocarbonyloxy)-N,N,N-trimethylethanaminium chloride

Figure 9: Structures of common quaternary ammonium salt used in DES.

ChCl is the most common quaternary ammonium salt used with DES. It is a low cost, nontoxic compound. In addition, it is classified as a provitamin in Europe and produced on large scale as an animal feed supplement.[19] When mixing ChCl with a hydrogen-donor such as urea, the hydrogen bonding between ChCl and urea is responsible for reaching the eutectic point (Figure 10). At the eutectic point, the melting point of the forming mixture is significantly lower than the melting points of the individual components. The sharp reduction in melting points is believed to be caused by the charge delocalization due to the hydrogen bonding between the complex components, which results in lower lattice energy.[18-20] For example, the melting point of choline chloride is 303 °C and for urea is 134 °C, while the melting point of the choline chloride:urea mixture is 12 °C (in 1:2 molar ratio).[20]

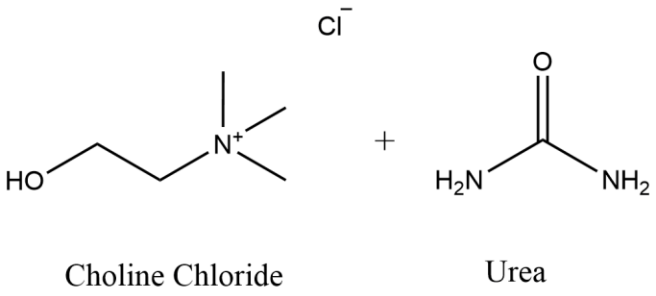
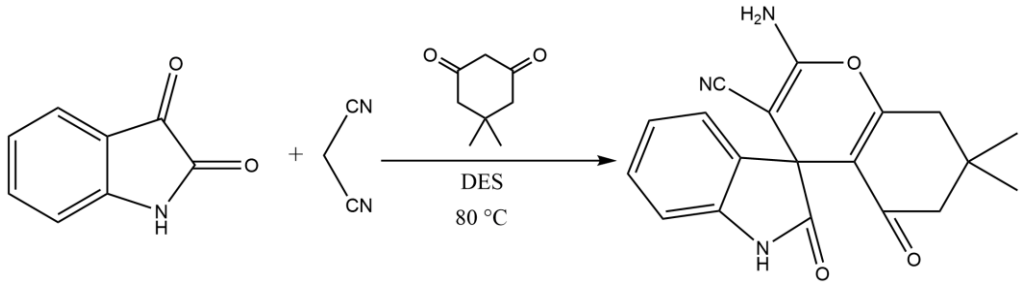


Figure 10: Choline Chloride:Urea.

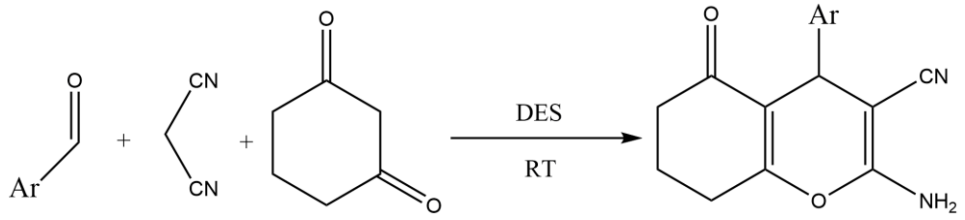
Employing DES in MCR

Recently, DES have begun to be employed in MCR, particularly in the reactions initiated by a Knoevenagel condensation followed by Michael addition. For instance, Azizi *et al.* reported the MCR of aromatic aldehydes, malononitrile, and dimedone at 80 °C in CC/U.[21] The reaction produced tetrasubstituted 4*H*-pyran derivatives in good yields (Scheme 10).



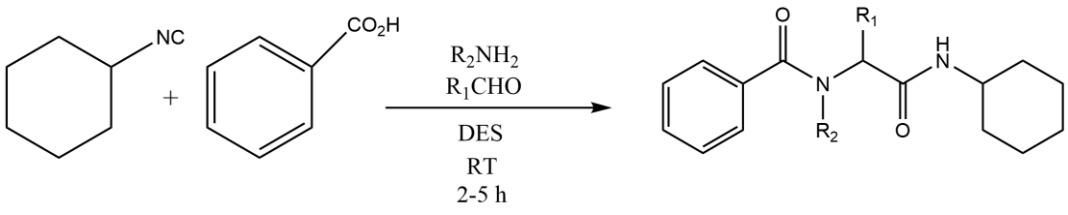
Scheme 10: MCR of aromatic aldehydes, malononitrile, and dimedone by Azizi *et al.*

Similar work has been reported by Mantelingu and co-workers at room temperature with high yields after 30 min (Scheme 11).[22] It is noteworthy to mention that the addition of the active methlylene in Mantelingu's work was 5 min after the reaction of other component had begun.



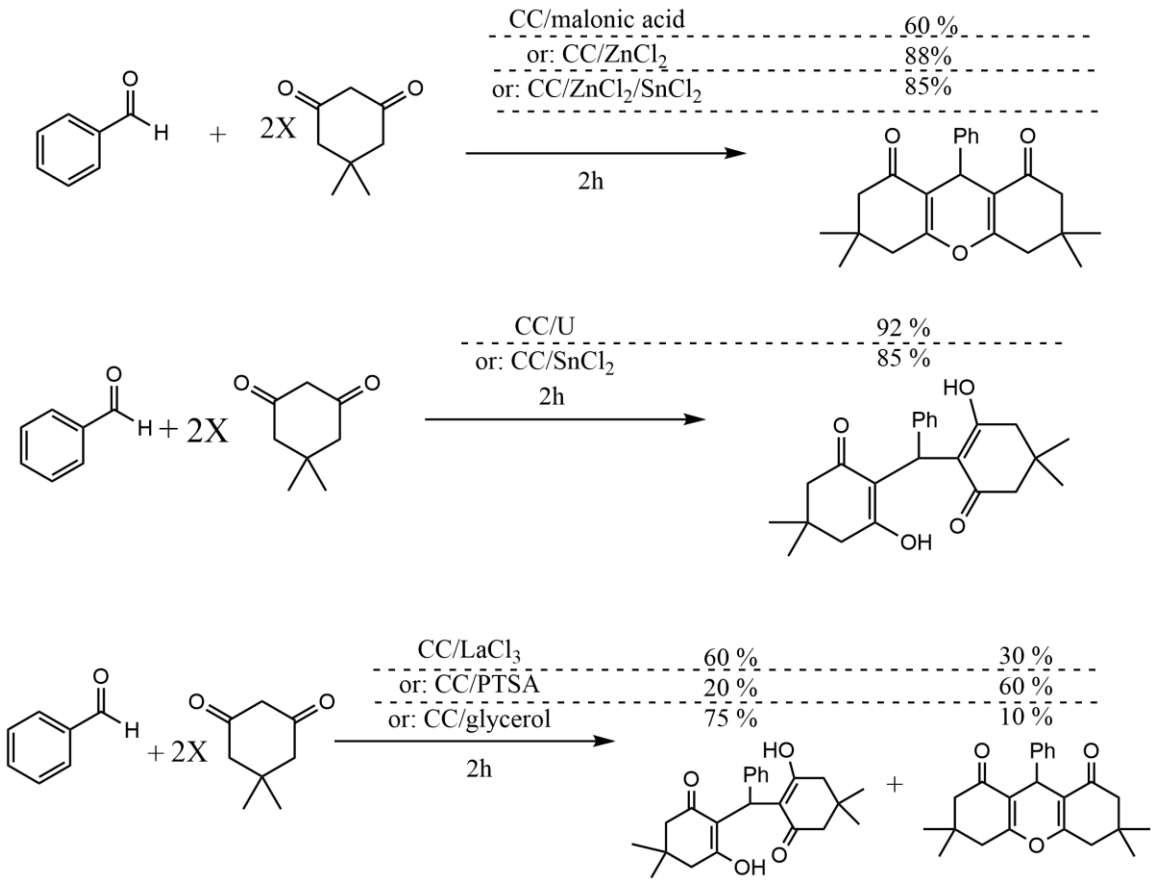
Scheme 11: MCR by Mantelingu and co-workers.

The classical Ugi reaction has also been reported in CC/U (Scheme 12).[23] This paper compared the yield when using CC/U as a solvent with the outcomes from several organic solvents (ethanol, methylene chloride, acetonitrile, water, and solvent-free conditions). The use of a DES afforded much higher yields than did the other organic solvents, water, or solvent-free conditions.



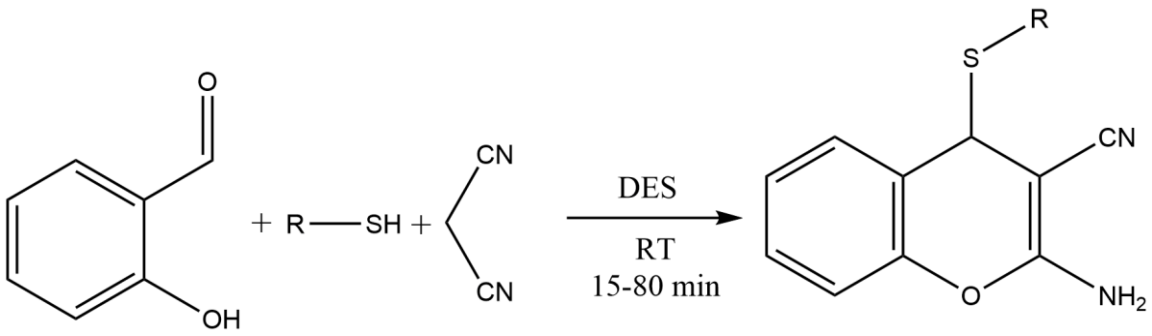
Scheme 12: The classical Ugi reaction in CC/U solvent.

One of the important papers on MCR in DES studied the condensation of aldehydes with dimedone or cyclohexane-1,3-dione (Scheme 13).[17] This study shows that the choice of DES directs the reaction and determines the major product. In CC/U media, a very high yield of the ring-open product was formed. Alternatively, the use of choline chloride/$ZnCl_2$ (CC/$ZnCl_2$) produced only the closed ring form in good yield, while the use of choline chloride/$SnCl_2$ (CC/$SnCl_2$) produced only the open ring form in good yield. In addition, choline chloride/glycerol (CC/G) and Choline chloride/p-toluene sulfonic acid (CC/PTSA) afforded a mixture of the two products. The reported study shows the importance of the choice of DES and an interesting opportunity to tune selectivity based upon selection of solvent.



Scheme 13: The selectivity of some MCR depending upon DES.

Another paper reported on MCR in CC/U starts with condensation of malononitrile with salicylaldehyde, then followed by Michael addition (Scheme 14).[24] This work has many advantages such the good yield, short reaction time, and easy work-up procedure.



Scheme 14: The MCR reaction of malononitrile, salicylaldehyde and thiols in CC/U

Current project

Although most of the reported work offers distinct advantages, they also suffer from certain drawbacks, such as longer reaction times, high costs, and the use of high amounts of environmentally toxic or expensive catalysts. Thus, considering the above importance of 2-amino-3-cyano-*4H*-pyran derivatives and the need for the development of new environmentally friendly synthetic methodologies, the combination of MCR and DES was the goal of our study in order to make the reaction more environmentally, as well as economically, viable.

CHAPTER II

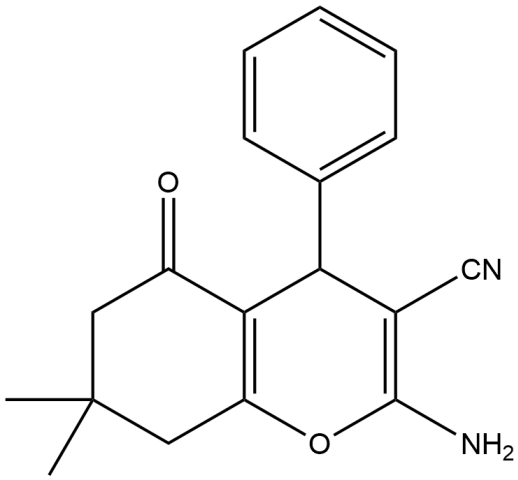
EXPERIMENTAL

All ^{1}H NMR spectra were collected using a JEOL 500 MHz or JEOL 300 MHz spectrometer using DMSO–d6 as solvent and the chemical shifts values reported in δ (ppm). Reagents used in the experiments were purchased from Alfa Aesar, Sigma Aldrich, or Eastman Organic Chemical. All reactions were carried out in a 20 mL capsule style glass vial.

Preparation of choline chloride/urea (CC/U)

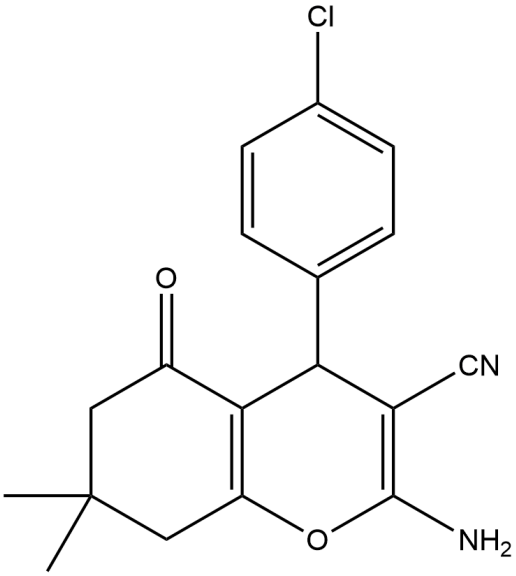
Choline chloride (7 g, 50 mmol) and urea (6 g, 100 mmol) were mixed in a 20 mL capsule style glass vial to form a 1:2 molar mixture. The vial was placed on MaxQ™ 2000 Benchtop Orbital Shaker equipped with a J-Kem 3300 thermocouple. The shaker was allowed to run overnight at 70.8°C. Eventually, the mixture formed a clear liquid, which was kept at the same temperature and used as reaction media when needed.

2-Amino-4-phenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



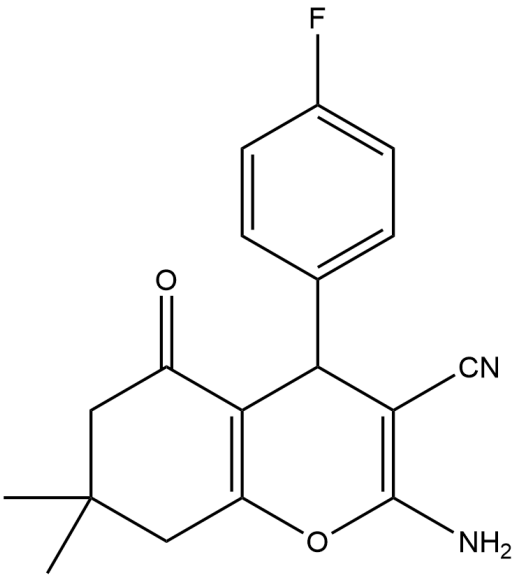
To a reaction vessel was added 0.318 g (3.00 mmol) benzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a sand bath and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.385 g (43.7%) of the desired product as a white solid (mp 228-230 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.25 (t, 2H), 7.17 (t, 1H), 7.11 (d, J = 6.8 Hz, 2H), 6.98 (s, 2H), 4.14 (s, 1H), 2.49 (s, 2H), 2.24 (d, J = 16.0 Hz, 1H), 2.08 (d, J = 16.0 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H).

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



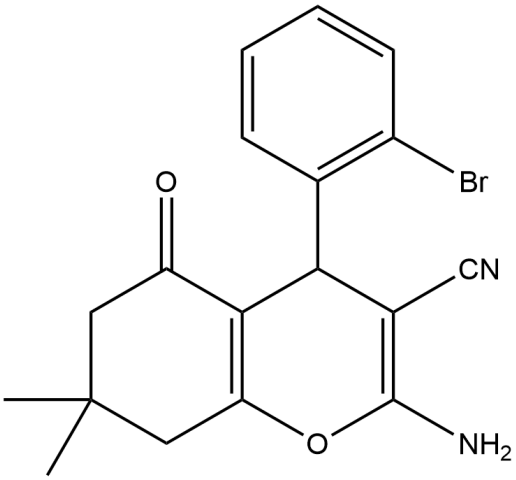
To a reaction vessel was added 0.337 g (3.00 mmol) 4-chlorobenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.449 g (45.7%) of the desired product as a yellow solid (mp 208-210 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.33 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.05 (s, 2H), 4.17 (s, 1H), 2.49 (s, 2H), 2.23 (d, *J* = 16 Hz, 1H), 2.08 (d, J = 16 Hz, 1H), 1.02 (s, 3H), 0.93 (s, 3H).

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



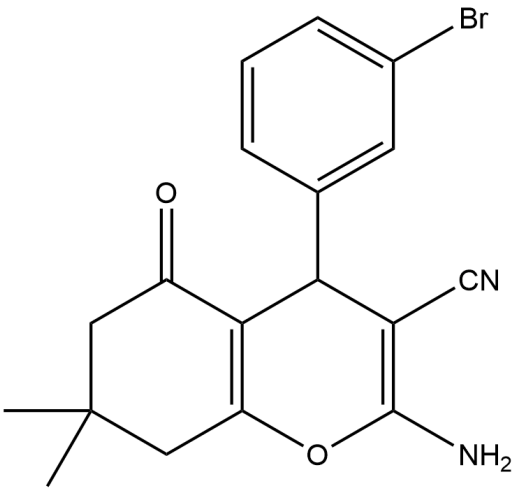
To a reaction vessel was added 0.372 g (3.00 mmol) 4-fluorobenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.557 g (59.6%) of the desired product as a white solid (mp = 210-212 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.38 (d, J = 6.8 Hz, 2H), 7.28-7.25 (m, 2H), 7.14 (d, J = 7 Hz, 2H), 7.09 (s, 2H), 4.18 (s, 1H), 2.49 (s, 2H), 2.24 (d, *J* = 16 Hz, 1H), 2.11 (d, *J* = 16 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H).

2-Amino-4-(2-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [8]



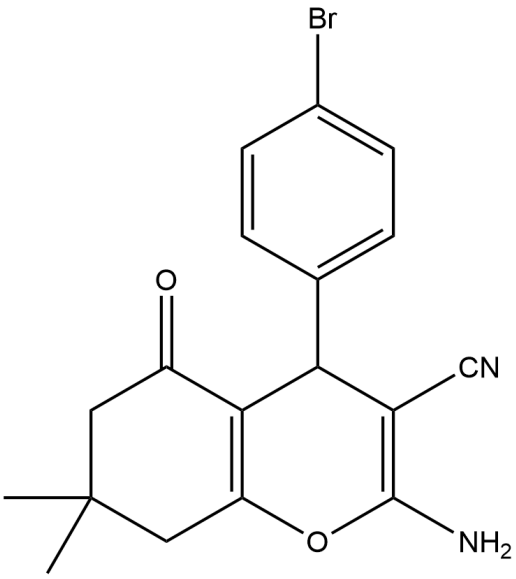
To a reaction vessel was added 0.555 g (3.00 mmol) 2-bromobenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.217 g (19.4%) of the desired product as a white solid (mp = 202-204 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.46 (d, *J* = 8.59, 2H), 7.09 (d, *J* = 8.02, 1H), 7.05 (s, 1H), 4.36 (d, *J* = 5.15, 1H), 4.16 (s, 1H), 2.49 (br s, 2H), 2.25-2.21 (d, *J* = 16 Hz, 1H), 2.10-2.07 (d, *J* = 16 Hz, 1H), 1.02 (s, 3H), 0.93 (s, 3H).

2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



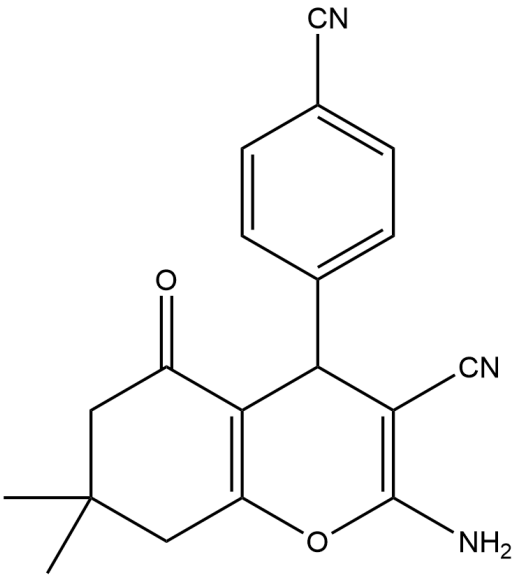
To a reaction vessel was added 0.555 g (3.00 mmol) 3-bromobenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.655 g (58.6%) of the desired product as an off-white solid (mp = 210-216 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.17-7.07 (m, 4H), 7.01 (s, 2H), 4.18 (s, 1H), 2.48 (s, 2H), 2.23 (d, *J* = 16 Hz, 1H), 2.09 (d, *J* = 16 Hz, 1H), 1.02 (s, 1H), 0.93 (s, 1H).

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



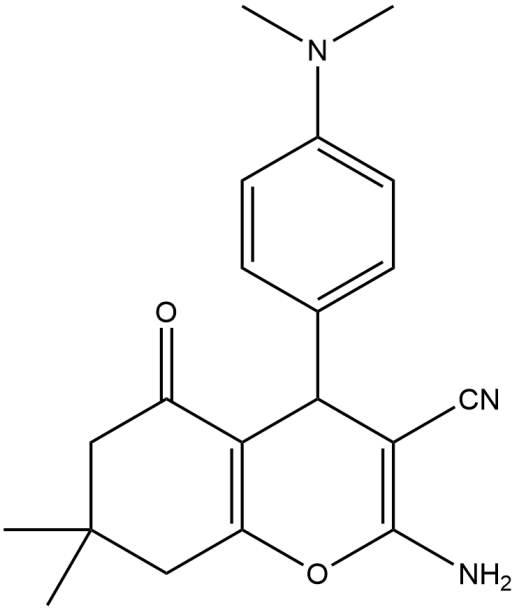
To a reaction vessel was added 0.555 g (3.00 mmol) 4-bromobenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.605 g (54.1%) of the desired product as a yellow solid (mp = 200-204 ^{o}C). ^{1}H NMR (300 MHz, DMSO-*d6*): δ 7.44 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 7.04 (s, 2H), 4.14 (s, 1H), 2.47 (s, 2H), 2.21 (d, *J* = 16 Hz, 1H), 2.06 (d, *J* = 16 Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H).

2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



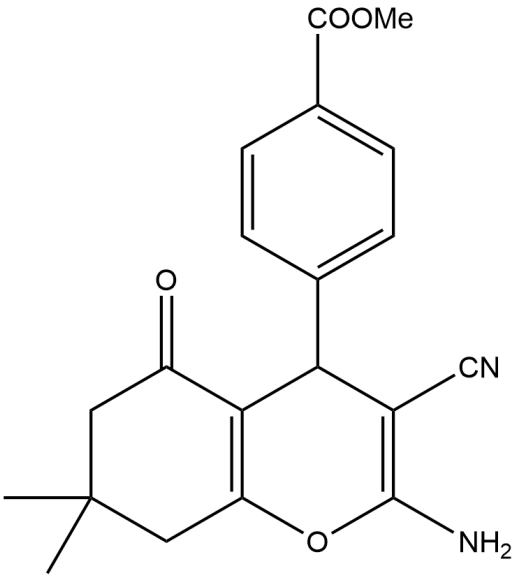
To a reaction vessel was added 0.393 g (3.00 mmol) 4-formylbenzonitrile, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.277 g (29%) of the desired product as a white solid (mp = 224-226 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.73 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.11 (s, 2H), 4.25 (s, 1H), 2.46 (s, 2H), 2.21 (d, *J* = 16 Hz, 1H), 2.07 (d, *J* = 16 Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H).

2-Amino-4-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [30]



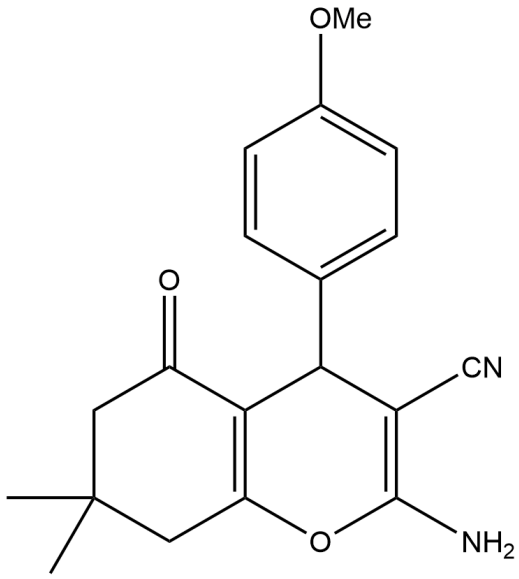
To a reaction vessel was added 0.447 g (3.00 mmol) 4-(Dimethylamino)benzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.697 g (69%) of the desired product as a turmeric yellow solid (mp = 218-220 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 6.90 (d, J = 9.1 Hz, 2H), 6.85 (s, 2H), 6.59 (d, J = 8 Hz, 2H), 4.00 (s, 1H), 2.80 (s, 6H), 2.46 (br s, 2H), 2.20 (d, 1H, *J* = 16.6 Hz), 2.04 (d, 1H, *J* = 16 Hz), 0.99 (s, 3H), 0.91 (s, 3H).

2-Amino-4-(4-carboxymethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [27]



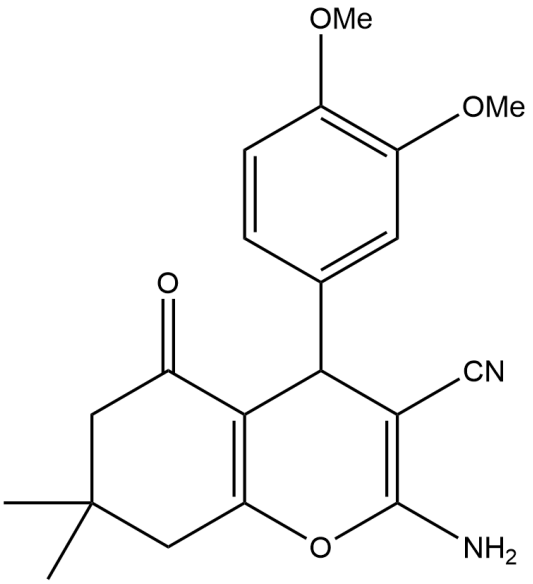
To a reaction vessel was added 0.492 g (3.00 mmol) methyl 4-formylbenzoate, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ºC. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.683 g (64.7%) of the desired product as an off-white solid (mp = 256-260 ºC). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.85 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 7.07 (s, 2H), 4.22 (s, 1H), 3.79 (s, 3H), 2.45 (br s, 2H), 2.22 (d, *J* = 16 Hz, 1H), 2.06 (d, *J* = 15.4 Hz, 1H), 0.99 (s, 3H), 0.89 (s, 3H).

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



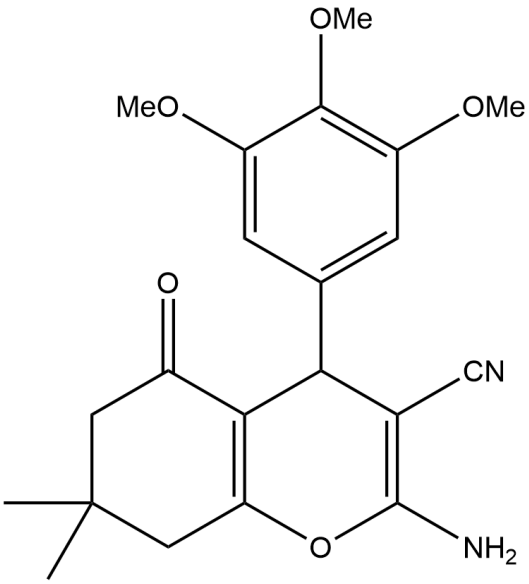
To a reaction vessel was added 0.408 g (3.00 mmol) 4-methoxybenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.469 g (48.3%) of the desired product as a yellow solid (mp = 194-196 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.03 (d, J = 7.6 Hz, 2H), 6.94 (s, 2H), 6.82 (d, J = 7.6 Hz, 2H), 4.09 (s, 1H), 3.69 (s, 3H), 2.48 (s, 2H), 2.22 (d, *J* = 16 Hz, 1H), 2.07 (d, *J* = 16 Hz, 1H), 1.01 (s, 3H), 0.92 (s, 3H).

2-Amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [15]



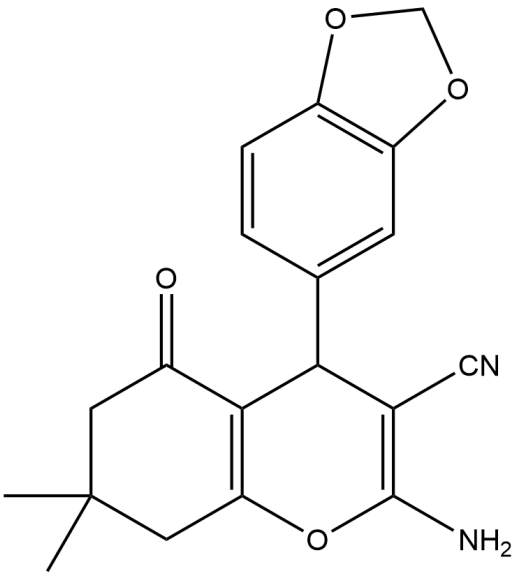
To a reaction vessel was added 0.498 g (3.00 mmol) 3,4-dimethoxybenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.641 g (60.4%) of the desired product as a yellow solid (mp = 164-168 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 6.94 (s, 2H), 6.85 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.63 (dd, J = 2.2, 6.3 Hz, 1H), 4.03 (s, 1H), 3.69 (s, 3H), 3.38 (s, 3H), 2.49 (s, 2H), 2.25 (d, J = 16 Hz, 1H), 2.12 (d, J = 16 Hz, 1H), 1.02 (s, 3H), 0.96 (s, 3H).

2-Amino-4-(3,4,5-trimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [29]



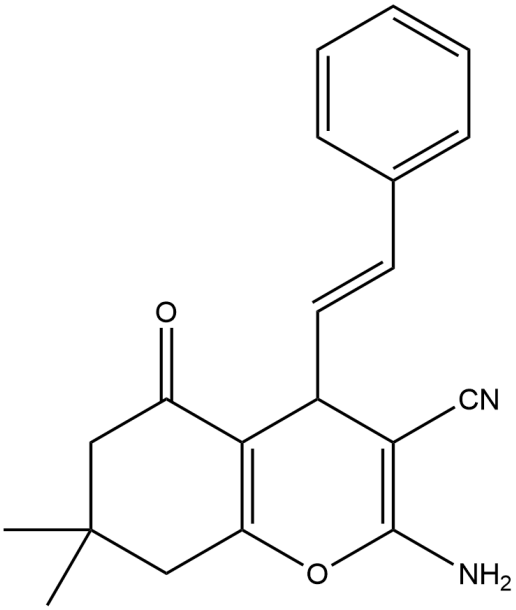
To a reaction vessel was added 0.588 g (3.00 mmol) 3,4-dimethoxybenzaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.843 g (73.2%) of the desired product as a white solid (mp = 164-168 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*):6.94 (s, 2H), 6.35 (s, 2H), 4.10 (s, 1H), 3.68 (s, 6H), 3.59 (s, 3H), 2.47 (s, 2H), 2.26 (d, J = 16 Hz, 1H), 2.11 (d, J = 16 Hz, 1H), 1.2 (s, 3H), 1.00 (s, 3H).

2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



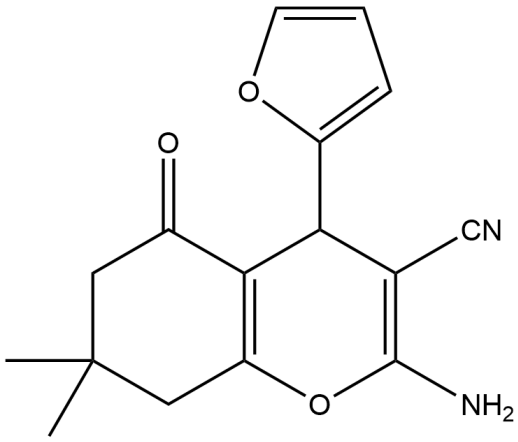
To a reaction vessel was added 0.450 g (3.00 mmol) piperonal, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.612 g (60.4%) of the desired product as an off-white solid (mp = 204-210 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 6.95 (s, 2H), 6.77 (dd, J = 8.02 Hz, 1H), 6.61 (s, 1H), 6.57 (d, J = 8.02 Hz, 1H), 5.93 (s, 2H), 4.07 (s, 1H), 2.46 (s, 2H), 2.20 (d, *J* = 16 Hz, 1H), 2.08 (d, *J* = 16 Hz, 1H), 0.99 (s, 3H), 0.92 (s, 3H).

2-Amino-4-(2-phenylethenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [28]



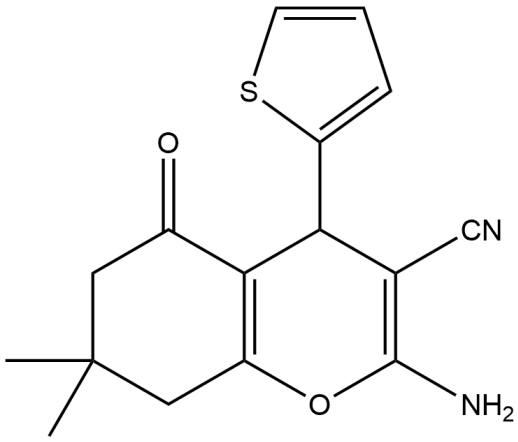
To a reaction vessel was added 0.396 g (3.00 mmol) cinnamaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.198 g (20.7%) of the desired product as a yellow solid (mp = 194-196 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.37-7.2 (m, 6H), 7.05 (s, 2H), 6.34 (d, *J* = 15 Hz, 1H), 6.06 (d, *J* = 15 Hz, 1H), 4.02 (s, 1H), 2.83 (s, 6H), 2.49 (q, 2H), 2.28-2.25 (d, *J* = 16 Hz, 1H), 2.09-2.04 (d, *J* = 16 Hz, 1H), 1.01 (s, 1H), 0.93 (s, 1H).

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [25]



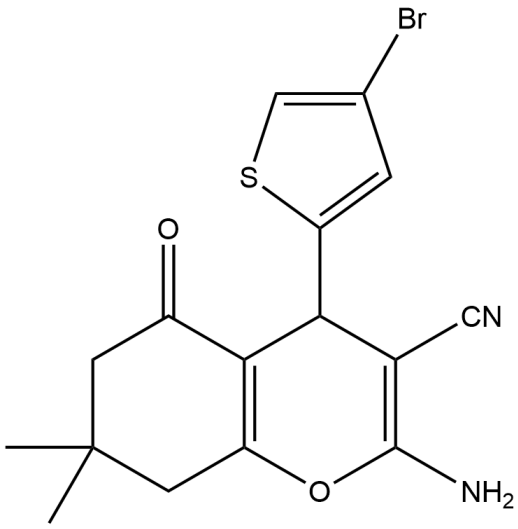
To a reaction vessel was added 0.288 g (3.00 mmol) 2-furaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.214 g (25.13%) of the desired product as a black solid (mp = 210-212 ^{o}C). ^{1}H NMR (300 MHz, DMSO-*d6*): δ 7.46 (br s, 1H), 7.07 (s, 2H), 6.31 (br s, 1H), 6.03 (br s, 1H), 4.31 (s, 1H), 2.49 (br s, 2H), 2.26 (d, *J* = 16 Hz, 1H), 2.15 (d, *J* = 16 Hz, 1H), 1.02 (s, 3H), 0.97 (s, 3H).

2-Amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile [26]



To a reaction vessel was added 0.336 g (3.00 mmol) 2-thiophenecarboxaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.368 g (40.9%) of the desired product as a dark brown solid (mp = 220-222 ^{o}C). ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.46 (d, J = 0.85 Hz, 2H), 7.07 (s, 2H), 6.31 (dd, J = 1.7, 3.45 Hz, 1H), 6.04 (d, J = 3.45, 1H), 4.30 (s, 1H), 2.48 (m, 2H), 2.27 (d, J = 16 Hz, 1H), 2.15 (d, J = 16 Hz, 1H), 1.03 (s, 3H), 0.97 (s, 3H).

2-Amino-7,7-dimethyl-5-oxo-4-(4-bromothiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile



To a reaction vessel was added 0.336 g (3.00 mmol) 4-bromo-2-thiophenecarboxaldehyde, 0.198 g (3.00 mmol) malononitrile, 0.420 g (3.00 mmol) dimedone, and 5.0 mL of a 1:2 molar mixture of CC/U as solvent. The vial placed on a hot plate and stirred overnight at 90 ^{o}C. After completion of the reaction, the vial was brought to room temperature, water was added and the precipitated solid was filtered. The crude product was recrystallized from hot ethanol to afford 0.352 g (31.1%) of the desired product as a dark brown solid (mp = 202-204 ^{o}C) ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.46 (s, 1H), 7.21 (s, 2H), 6.85 (s, 1H), 4.53 (s, 1H), 2.48 (s, 2H), 2.28 (d, J = 16 Hz, 1H), 2.15 (d, J = 16 Hz, 1H), 1.02 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (500 MHz, DMSO-*d6*) δ 195.5, 162.9, 158.7, 150.9, 126.1, 122.2, 119.0, 112.0, 107.7, 56.8, 49.7, 31.7, 30.2, 28.5, 26.4. IR : υ cm^{-1} 3447, 3388, 3328, 3192, 3104, 2958, 2186, 1659, 1597, 1372, 1207, 1137, 1032, 739, 720.

CHAPTER III
RESULTS AND DISCUSSION

Due to the previously mentioned importance of polyfunctionalized 2-amino-3-cyano-*4H*-pyran derivatives in biological and pharmacological applications, there is a need for developing new synthetic methods capable of providing easy access to a library of compounds and yet also reasonable for larger scale application. As discussed before, the combination of MCR and DES could lead to a more efficient method. Therefore, we studied this catalyst free one-pot multicomponent coupling reaction using CC/U as the reaction media.

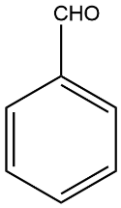
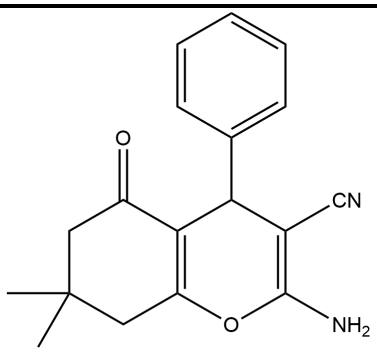
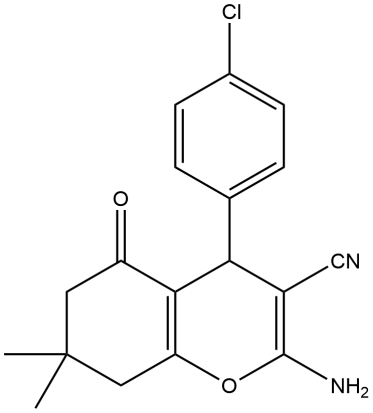
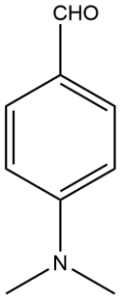
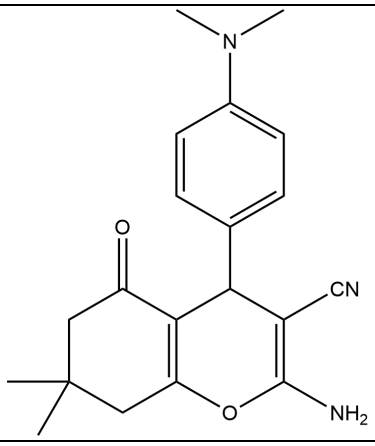
The synthesis of 2-amino-3-cyano-*4H*-pyran derivatives were achieved using an MCR approach and employing CC/U as an environmentally friendly solvent. The reactions were carried out at 90 ^{o}C without the need for base or catalyst, and the yields were good. A wide range of functionalized aromatic aldehydes have been studied in this work to determine the effectiveness of this procedure compared with what has been reported in the literature.

One of the first challenges encountered was the lack of careful evaluation for the reaction conditions of the synthesis of 2-amino-3-cyano-*4H*-pyran derivatives as well as poorly documented and inconsistent physical and spectral properties. Further, even though there are many papers reporting a synthesis of this class of compounds, there is little discussion of the mechanism and even less evidence. One general observation has been with respect to the reaction temperature.[21,29] It is generally believed that the temperature plays important role in the yields and reaction time. For instance, both Aziz

et al. and Pawar *et al.* reported that the yields increase with increasing temperature up to 80 ^{o}C. These results provide confirmatory evidence that the reaction will give the best yield when the temperature is at least 80 ^{o}C. On the basis of this evidence, we ran our first reaction overnight at 90 ^{o}C and continued on with the same conditions to normalize our outcome.

At the beginning, a one mmol scale was executed. The yield was lower than expected (35.7% in the case of the reaction with benzaldehyde, entry 1, Table 2), even though the proton NMR of the crude reaction mixture following extraction looked relatively clean. Based on our evaluation of the NMR spectra of the crude, there was a concern about the role of the purification method in the isolated yield. Recrystallization at 1 mmol scale is a challenge, which could be the reason for the low yield. Moreover, in case of the electron withdrawing groups (EWG) on the aldehyde, we had to use a binary solvent system (ethanol:water) in the recrystallization to obtain a crystalline precipitate. From there, we carried out a couple of reactions on a 3 mmol scale to determine if the isolated yield is being reduced because of the purification method and the scale of the reaction. On the 3 mmol scale, there was a considerable increase in yield as seen in Table 2. One other interesting observation of this increase in scale was that at the 3 mmol scale, all purification was done successfully using ethanol without the need for water as a co-solvent.

Table 2: Comparison of the yield when increasing the reaction scale.

Entry	Aldehyde	Product	Isolated Yield 1 mmol (%)	Isolated Yield 3 mmol (%)
1			35.7	43.7
2			22	45.7
3			48.7	69

Based on those results (Table 2), we started exploring a variety of substituted aromatic as well as heteroaromatic aldehydes using the larger 3 mmol scale (Table 3). Generally, electron withdrawing groups (EWG) on the aldehyde produced lower yields comparing with the electron donating groups (EDG) (Table 3, compare entries 7 and 8). In the case of a mild EWG such 4-fluorobenzaldehyde or 4-bromobenzaldehyde the yields ranged around 54-59% (Table 2, entries 3 and 4). The yields dropped further when using aldehydes with stronger EWG such as 4-formylbenzonitrile (Table 2, entry 7), and the reactions of 2-nitrobenzaldehyde and 3-nitrobenzaldehyde failed completely. On the other hand, there is a clear increase in yield when employing aldehydes with EDG. Several examples of EDG have been used including 4-(dimethylamino)benzaldehyde, piperonal, and 3,4,5-trimethoxybenzaldehyde (Table 2, entries 8, 13, and 12). In addition, an interesting trend appears with the methoxy substitutes. The yields increase steadily with increasing numbers of methoxy groups present. The yield of the 4-methoxybenzaldehyde is 48.3%, it goes up with 3,4-dimethoxybenzaldehyde to 60.4%, and it reaches 73.2% with 3,4,5-trimethoxybenzaldehyde. This trend supports the idea that the EDG positively influences the yields of this reaction.

Table 3: Multicomponent coupling reactions of 2-Amino-3-cyano-4*H*-pyran derivatives.

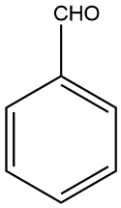
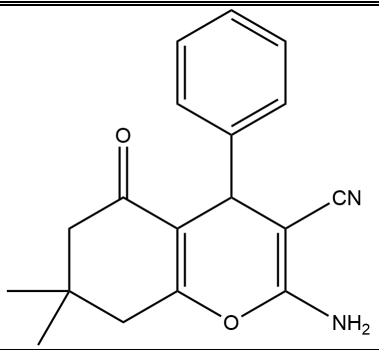
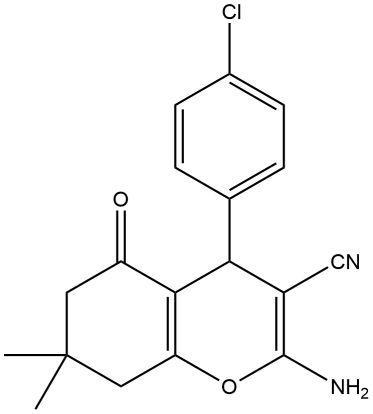
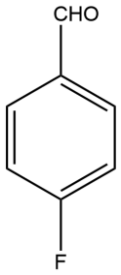
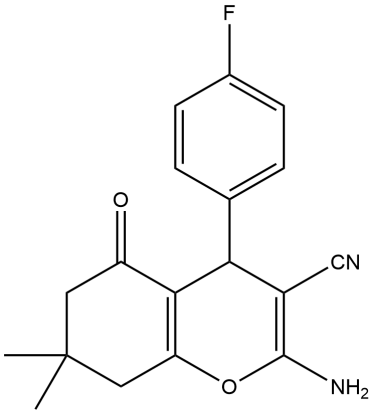
Entry	Aldehyde	Product	Isolated Yield (%)	Melting Point °C
1			43.7	228-230
2			45.7	208-210
3			59.6	210-212

Table 3 (cont.): Multicomponent coupling reactions of 2-Amino-3-cyano-4*H*-pyran derivatives.

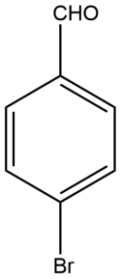
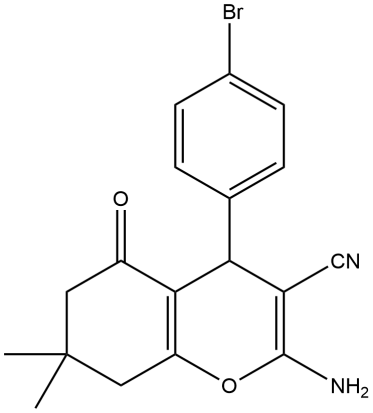
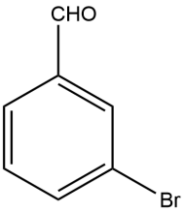
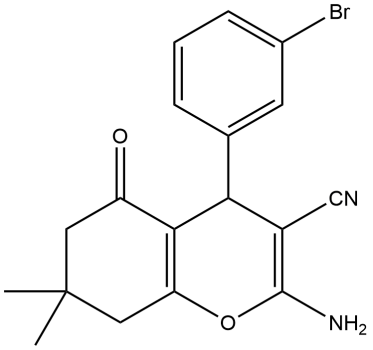
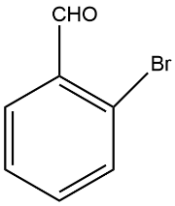
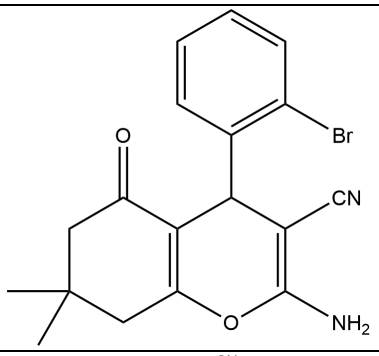
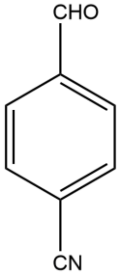
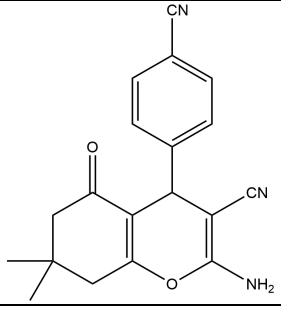
Entry	Aldehyde	Product	Isolated Yield (%)	Melting Point °C
4			54.1	200-204
5			58.6	210-216
6			19.4	202-204
7			29	224-226

Table 3 (cont.): Multicomponent coupling reactions of 2-Amino-3-cyano-4*H*-pyran derivatives.

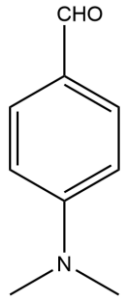
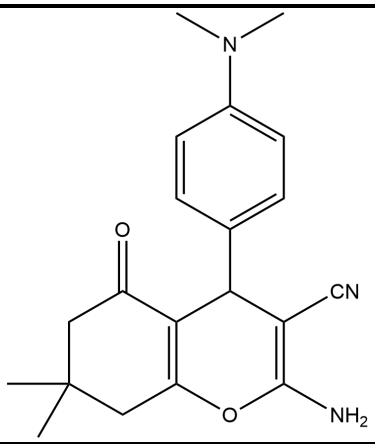
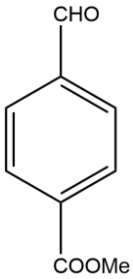
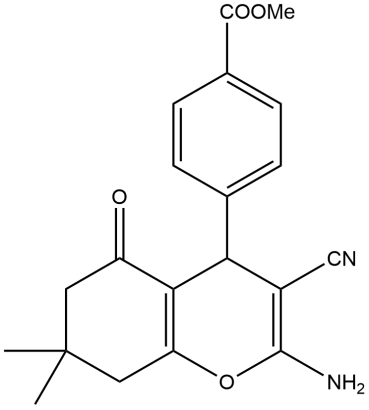
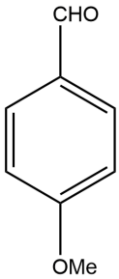
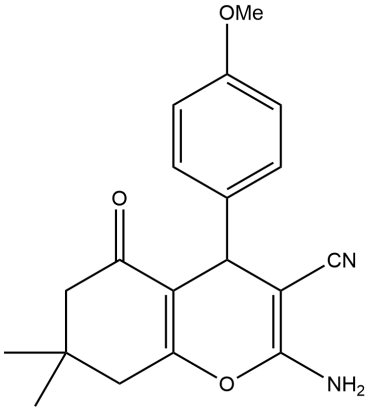
Entry	Aldehyde	Product	Isolated Yield (%)	Melting Point °C
8			69	218-220
9			64.7	256-260
10			48.3	194-196

Table 3 (cont.): Multicomponent coupling reactions of 2-Amino-3-cyano-4*H*-pyran derivatives.

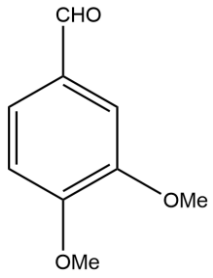
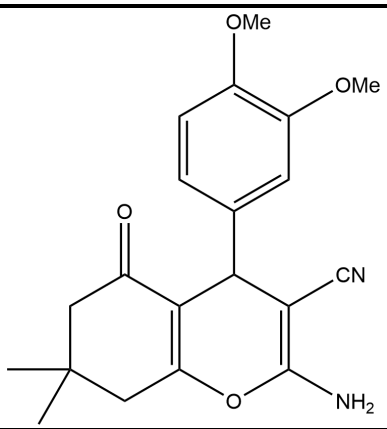
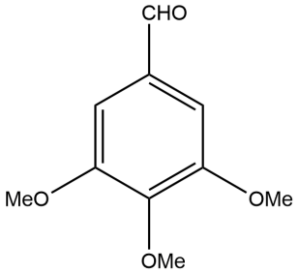
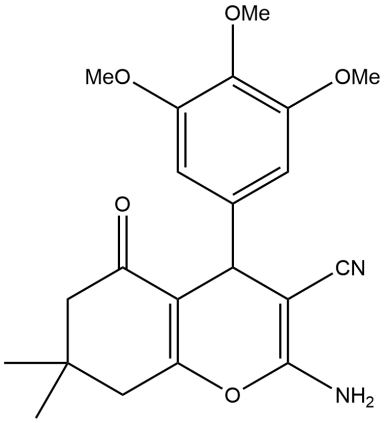
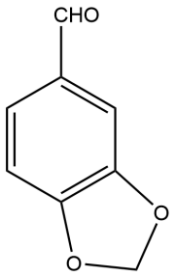
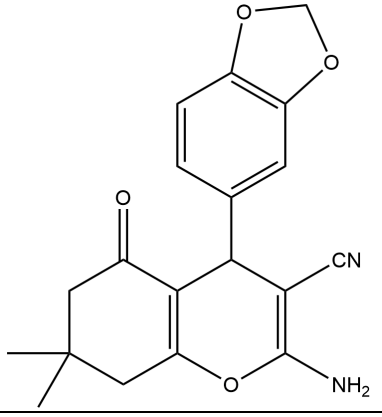
Entry	Aldehyde	Product	Isolated Yield (%)	Melting Point °C
11			60.4	164-168
12			73.2	164-168
13			60.4	204-210

Table 3 (cont.): Multicomponent coupling reactions of 2-Amino-3-cyano-4*H*-pyran derivatives.

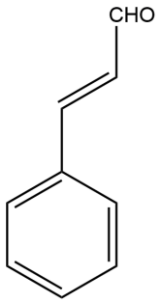
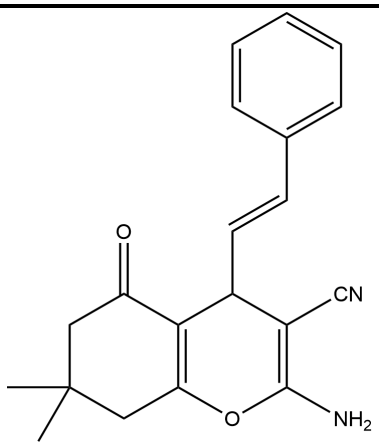
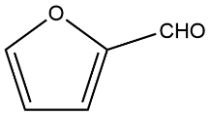
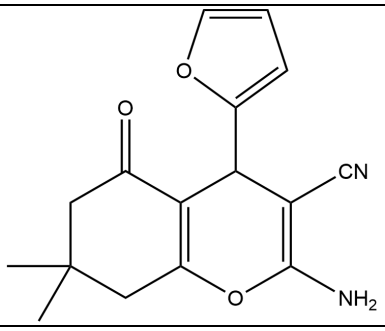
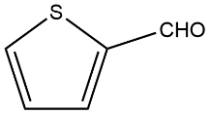
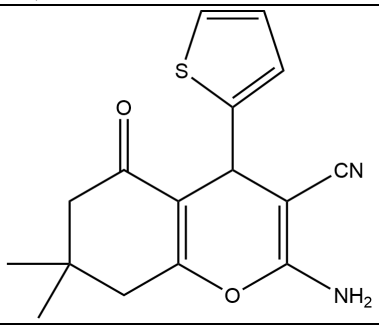
Entry	Aldehyde	Product	Isolated Yield (%)	Melting Point °C
14			20.7	194-196
15			25.13	210-212
16			40.9	220-222

Table 3 (cont.): Multicomponent coupling reactions of 2-Amino-3-cyano-4*H*-pyran derivatives.

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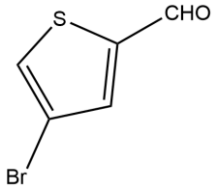
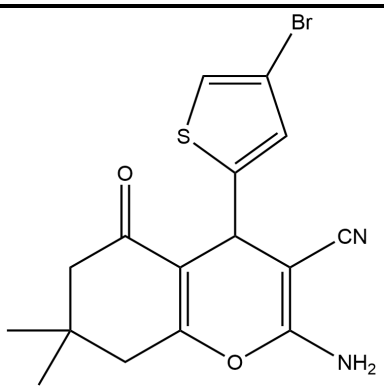
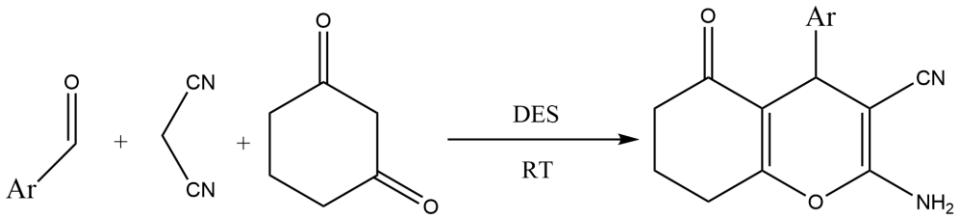
17			31.1	202-204

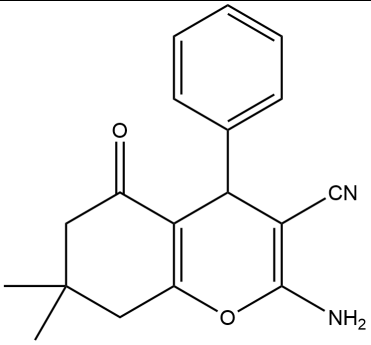
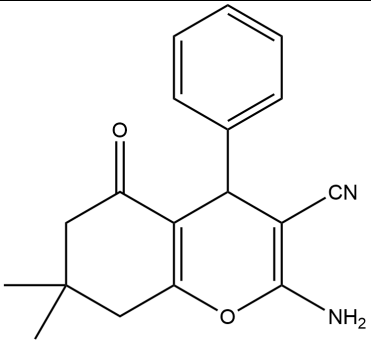
There were concerns regarding the yields even of the 3 mmol scale when compared with similar work reported in literature. The work reported by Mantelingu and co-workers is similar to our work and at room temperature with higher yields (Scheme 11). Mantelingu used cyclohexane-1,3-dione while we used dimedone. The very modest structural difference between these two diketones would not be expected to make a major difference in the isolated yields and efficiency of the reactions. One other difference was that the addition of the active methylene in Mantelingu's work was 5 min after the reaction of other component was initiated, while we added all three components simultaneously. This led us to consider that perhaps this difference in order of addition was significant and worthy of investigation.



Scheme 11: MCR by Mantelingu and co-workers.

To compare the procedure reported Mantelingu with our procedure we performed two trials (Table 4). In the first trial, we mixed benzaldehyde, malononitrile, and after five minutes, dimedone was added in accord with the Mantelingu procedure (Table 4, Entry 1). The second trial follows our standard method by adding benzaldehyde, malononitrile, and dimedone simultaneously (Table 4, Entry 2). Both reactions were run for 30 min at room temperature.

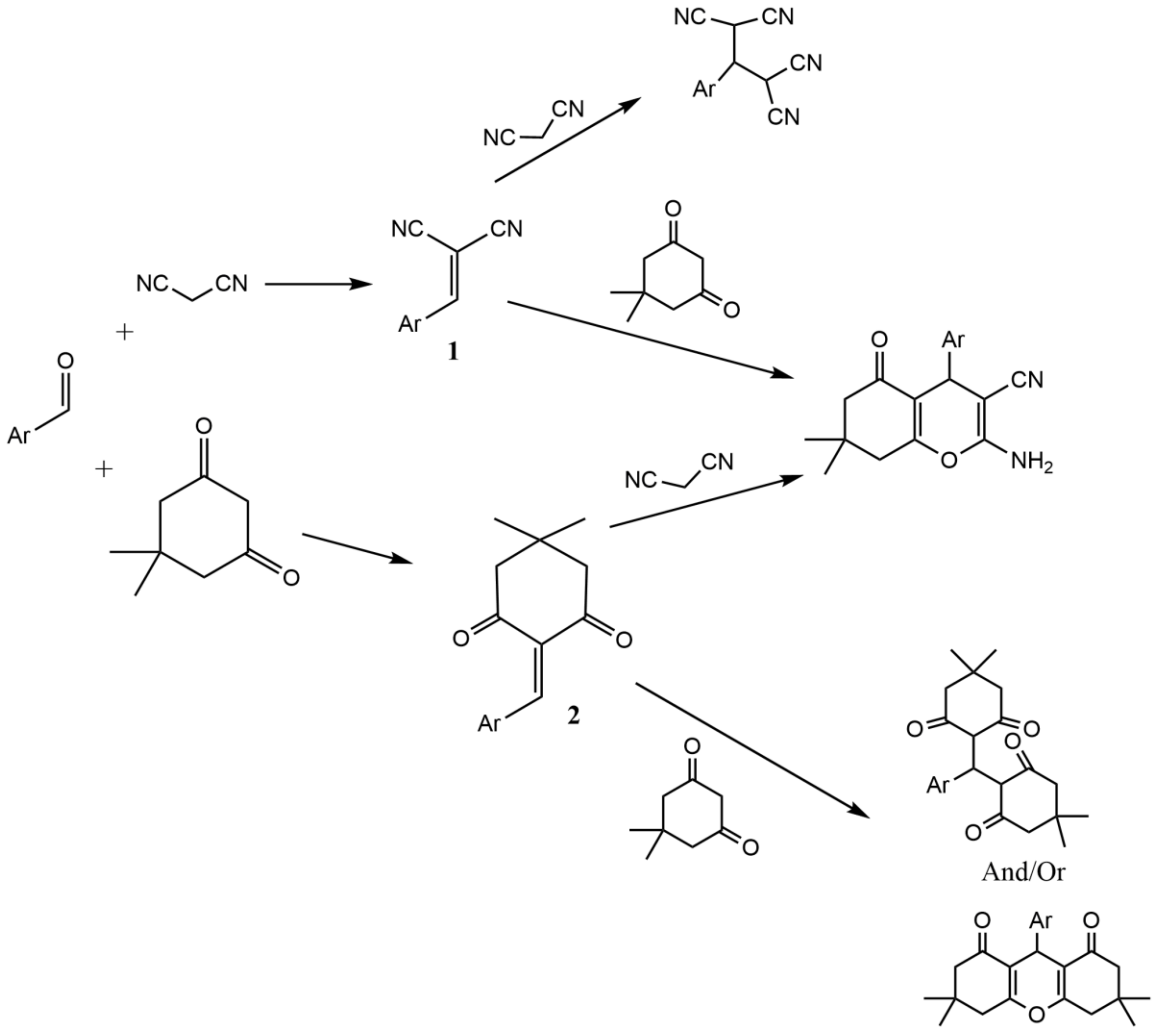
Table 4: Comparison of the procedure reported by Mantelingu with our procedure.

Entry	Product	Isolated Yield (%)	Comments
1		89%	Benzaldehyde, malononitrile, mixed together, and after five minutes, dimedone was added.
2		67%	All three components were mixed simultaneously.

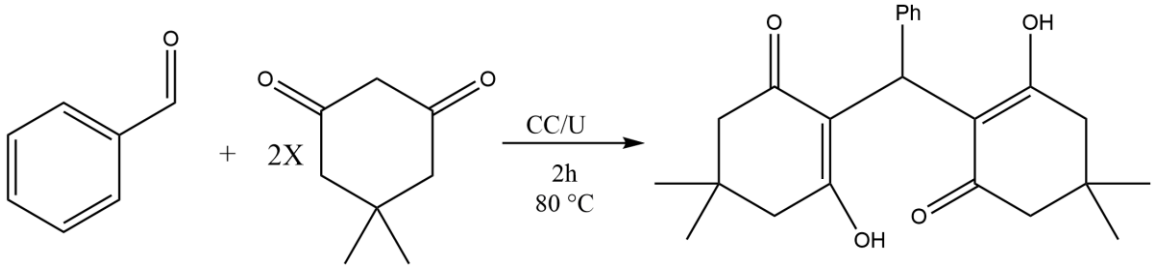
The first trial gave a bright white crude product and colorless aqueous layer. After recrystallization in ethanol, the yield was 89% (Table 4, Entry 1).

The second trial gave an orange crude product and the aqueous wash was orange. The yield was 67% after recrystallization in ethanol (Table 4, Entry 2). The reduction in yield and the color of the crude product both indicated that side reactions were competing with the desired reaction. A number of possible side reactions can be imagined, many of which are outlined in Scheme 15. With two active methylene compounds present along with the aldehyde, the initial condensation reaction could occur with malononitrile to afford intermediate **1**, or with dimedone to afford intermediate **2**. Malononitrile is the

more reactive active methylene compound and thus the route to **1** should dominate, but reaction with dimedone is also known, so **2** is possible as well.[23] With the intermediates formed, condensations can then result in at least 4 products. In point of fact, the number is likely larger as Azizi and co-workers have previously noted that condensation of dimedone with aldehydes in CC/U affords mixtures of the ring-open and ring-closed products (Scheme 16).[23] This competing reactivity is expected to be even worse at higher temperatures, which can be seen in the increase in yield of the desired product by going from 90 ^{o}C (44%, Table 2, entry 1) to room temperature (67%, Table 3, entry 2). Thus, application of the delay in addition and a decrease in reaction temperatures is expected to increase the yields of all of the reactions performed to date. This same modification would be expected to be beneficial to future multicomponent coupling reactions.



Scheme 15: Possible side reactions.



Scheme 16: Azizi MCR reaction.

CHAPTER IV

CONCLUSION

Polyfunctionalized 2-amino-3-cyano-4*H*-pyran derivatives have wide application in pharmacological field. Therefore, there is a need for developing new synthetic methods reasonable for larger scale application and environmentally benign. The procedure represented by this study uses a MCR approach and employs CC/U as an environmentally friendly solvent to produce 2-amino-3-cyano-4*H*-pyran derivatives. Therefore, we studied this catalyst free one-pot multicomponent coupling reaction using CC/U as the reaction media. Moreover, a simple work up procedure was developed via recrystallization from ethanol or ethanol-water to avoid the use of expensive silica gel chromatography and exclude the massive use of organic chromatography eluents. Finally, this work avoids the use of toxic and expensive catalyst or solvents.

Interestingly, increasing the reaction scale from 1 mmol to 3 mmol improved the reaction isolated yield. That increase in yield is believed to be due the effectiveness of recrystallization in 3 mmol scale, in order to purifying the product. On the 3 mmol scale, all purification was done successfully using ethanol without the need for water as a co-solvent, as some 1 mmol reactions required.

A variety of substituted aromatic as well as heteroaromatic aldehydes were explored using the larger 3 mmol scale. Generally, electron withdrawing groups (EWG) on the aldehyde produced lower yields comparing with the electron donating groups (EDG). In the case of a mild EWG such 4-fluorobenzaldehyde or 4-bromobenzaldehyde

the yields ranging around 54-59%. The yields dropped further when using aldehydes with stronger EWG such as 4-formylbenzonitrile. On the other hand, there is a clear increase in yield when employing aldehydes with EDG. Several examples of EDG have been used including 4-(Dimethylamino)benzaldehyde, piperonal, and 3,4,5-trimethoxybenzaldehyde. We can conclude that aromatic aldehydes that bearing EDG positively influences the yields of this reaction.

We ran a comparison between Mantelingu's method and our procedure. We have found that by mixing benzaldehyde, malononitrile, and adding dimedone after five minutes, in accordance with the Mantelingu procedure, produces a better yield. Also we have found that running the reaction at room temperature is suitable for CC/U, and produces better yield, thus providing clear evidence that CC/U is acting as a catalyst for these reactions, likely via hydrogen-bonding activiation.

In conclusion, the effectiveness of combining the aldehyde, active methylene, and adding nucleophile after five minutes has been proven. In other words, the delay in addition and a decrease in reaction temperatures are expected to increase the yields and limits any side-reactions that would compete with the desire reaction. This same modification would be expected to be beneficial to future multicomponent coupling reactions. In addition, employing different DES that produced only the closed ring form in high yield such as CC/$ZnCl_2$ and CC/$SnCl_2$ are worth investigating, although their greater water sensitivity may render them less satisfactory compared to CC/U.

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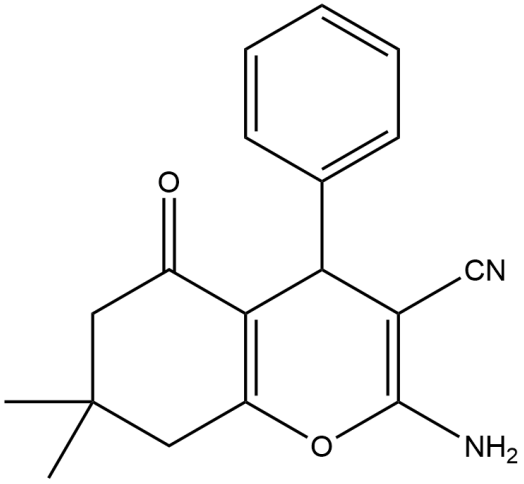
APPENDICES

APPENDIX A

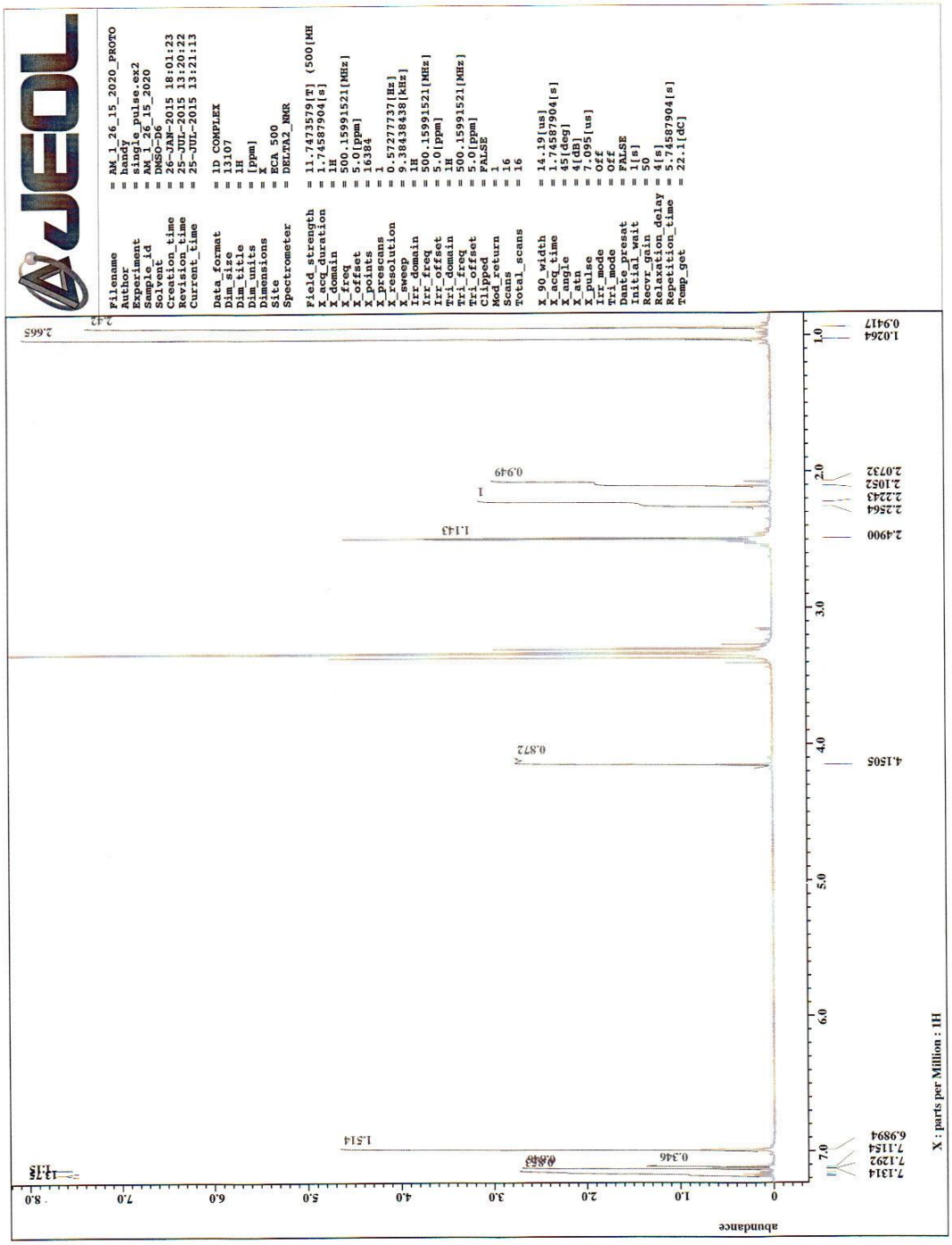
Spectroscopy Data

2-Amino-4-phenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile



NMR

^{1}H NMR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0.857
0.346
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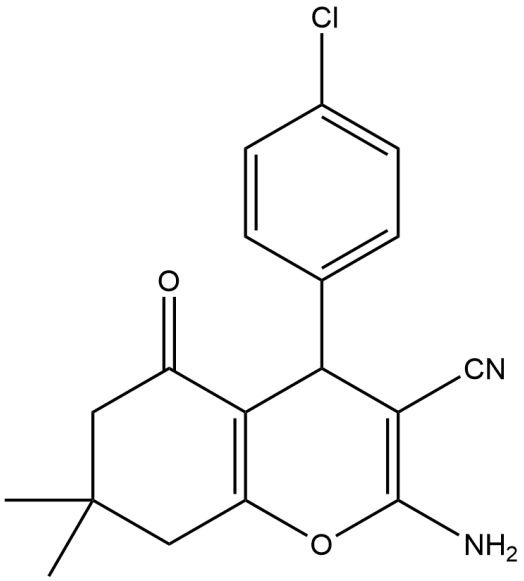
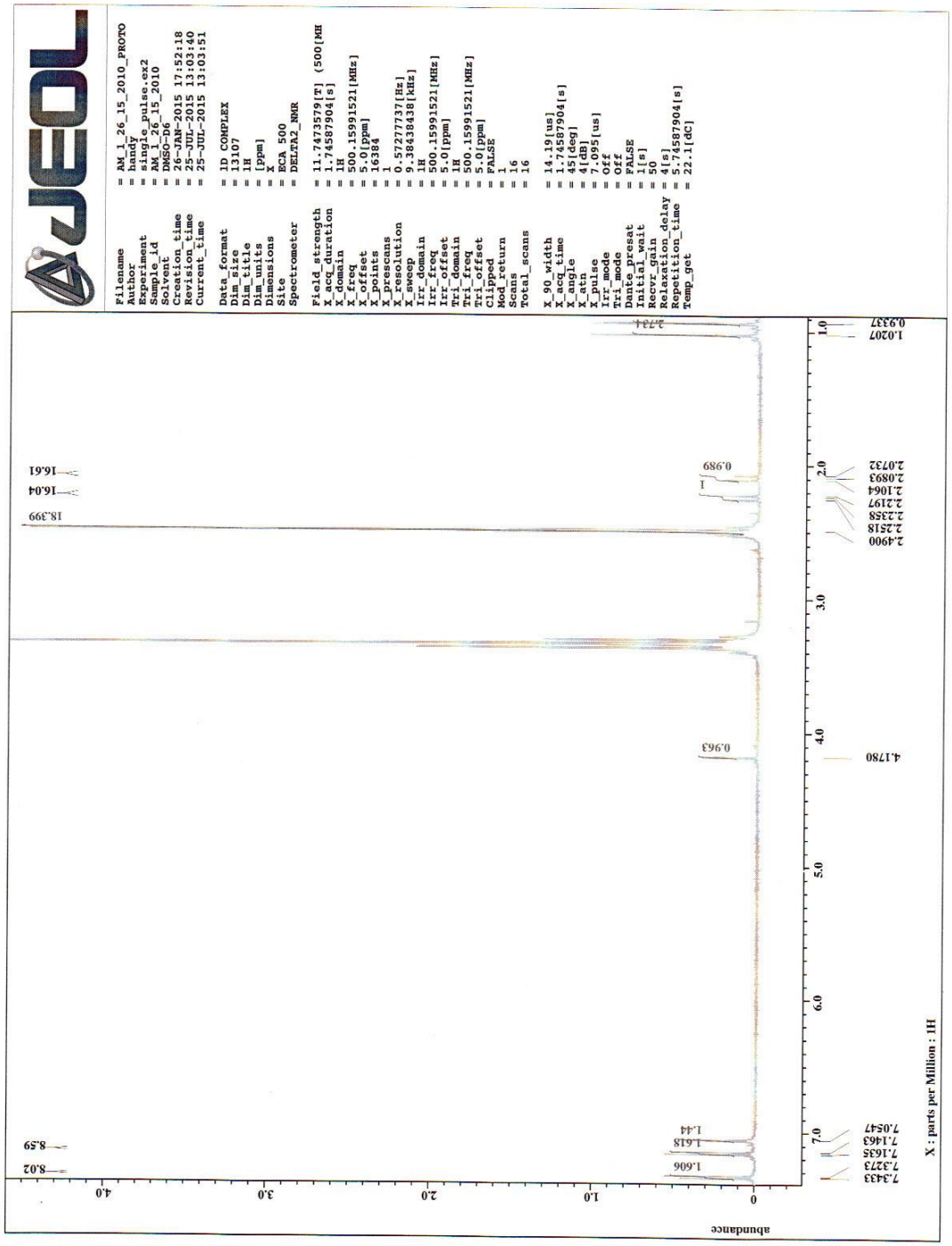
0.9417
2.0732
2.1052
2.2243
2.2564
2.4900
4.1505
7.1314
7.1292
7.1154
6.9894
abundance
X : parts per Million : 1H

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile



NMR

^{1}H NMR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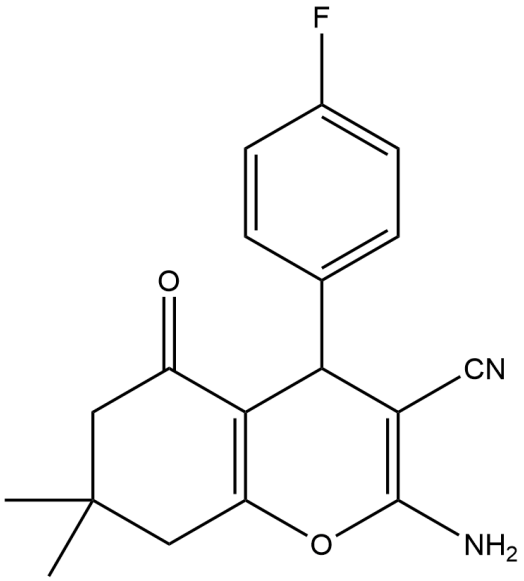

NMR

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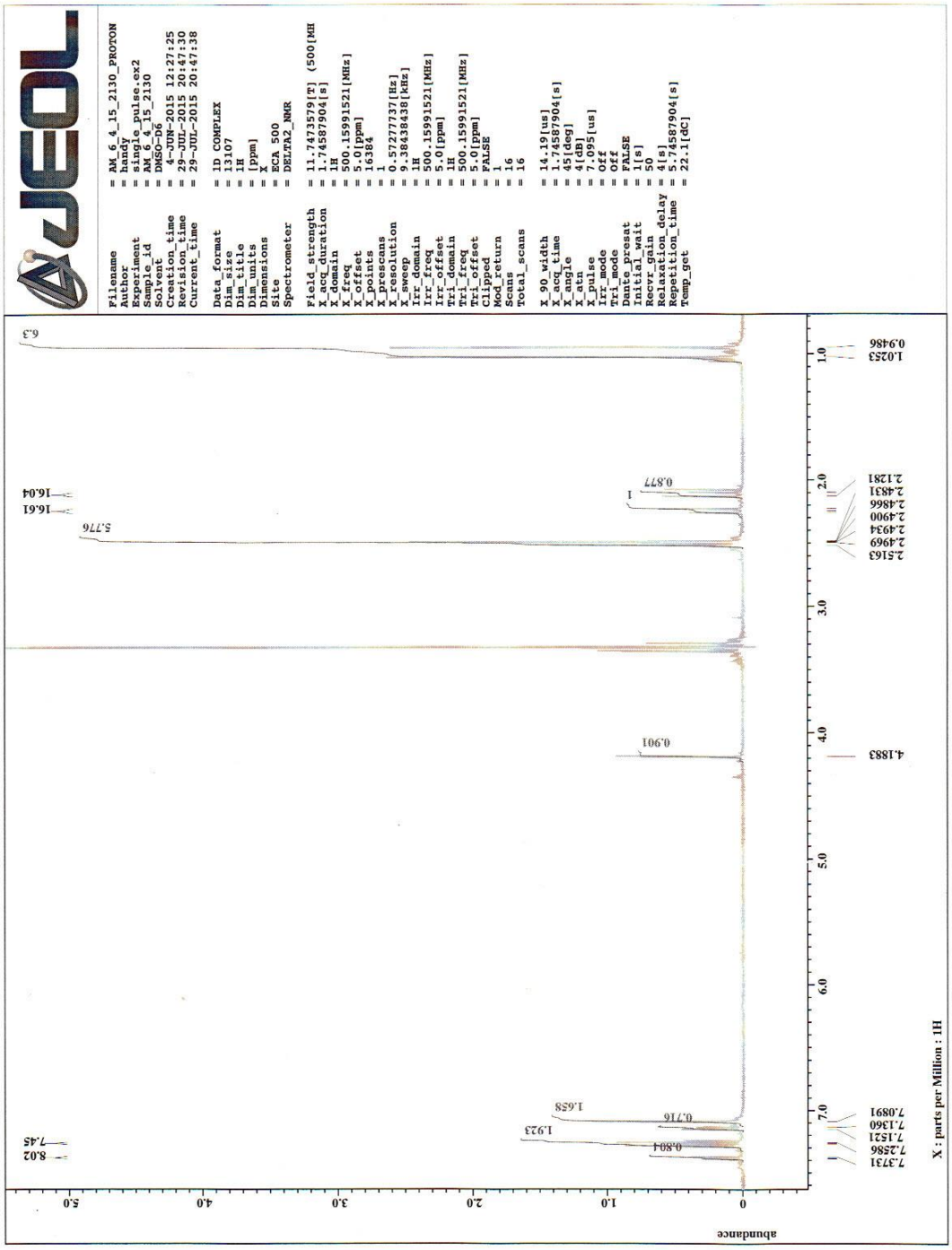
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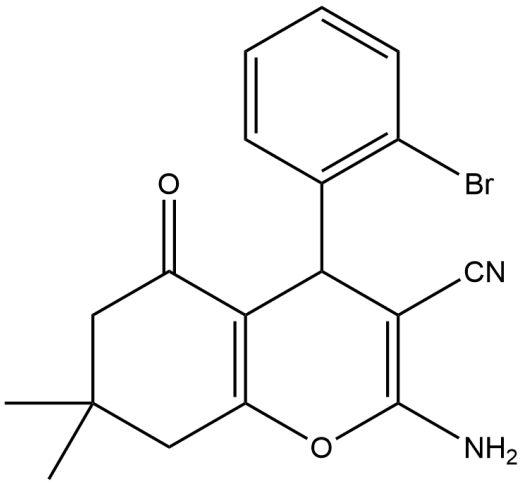
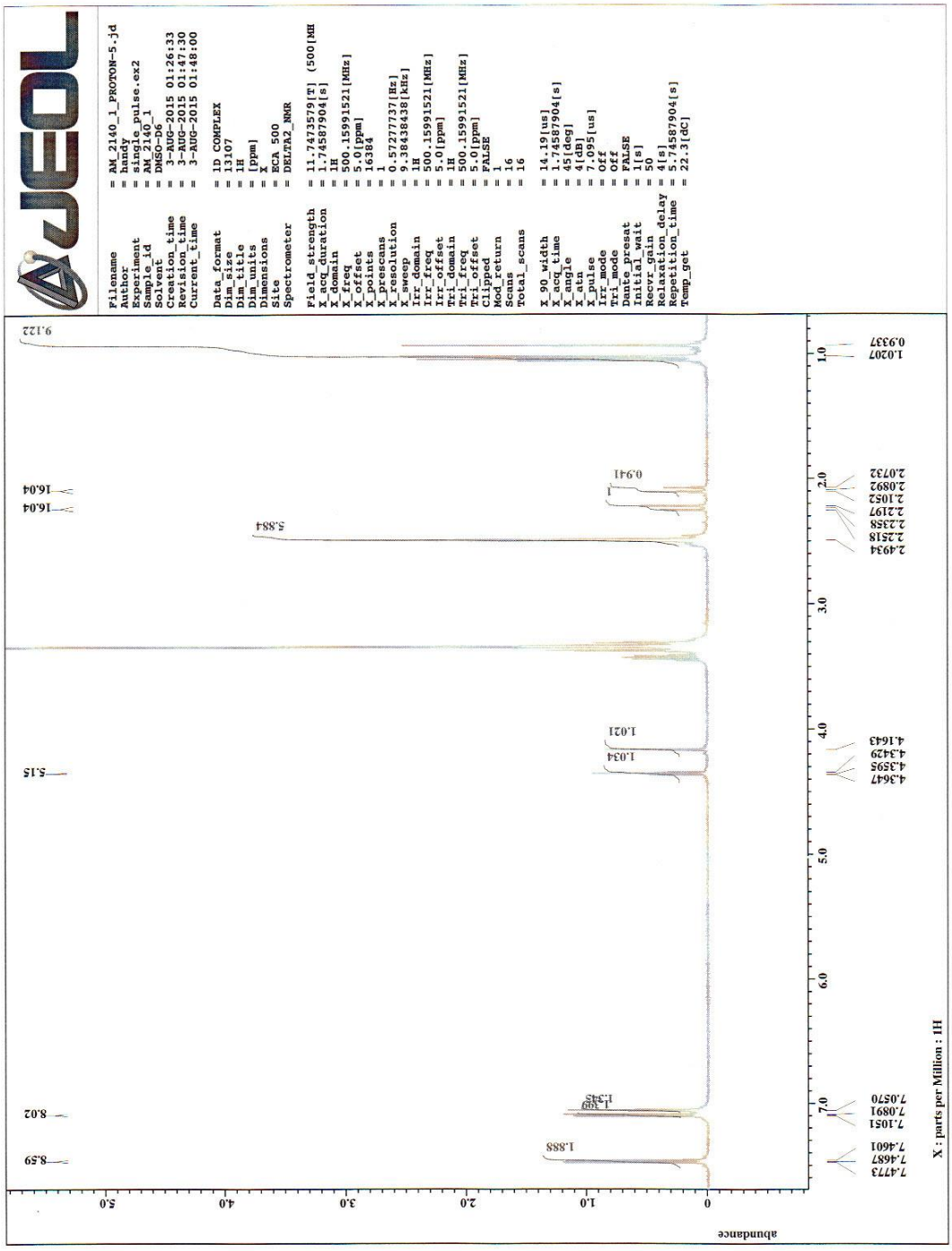
Revision_time = 29-JUL-2015 20:47:30
Current_time = 29-JUL-2015 20:47:38
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735791[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Decoupler_present = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 22.1[dC]
6.3
16.04
16.61
5.776
0.877
1
0.901
1.658
0.716
1.923
0.801
8.02
7.45
abundance
X : parts per Million : 1H
0.9486
1.0253
2.1281
2.4831
2.4866
2.4900
2.4934
2.4969
2.5163
4.1883
7.3731
7.2586
7.1521
7.1360
7.0891

2-Amino-4-(2-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

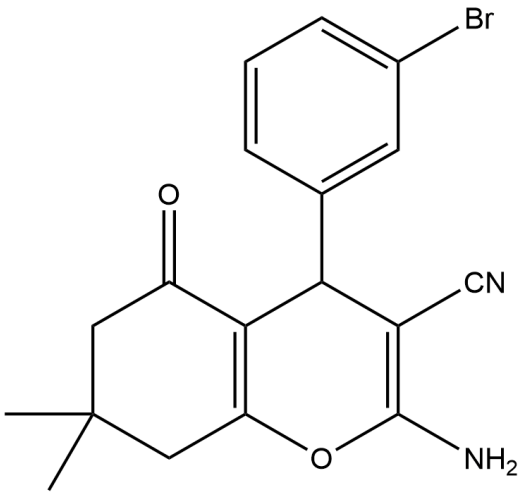


NMR

^{1}H NMR

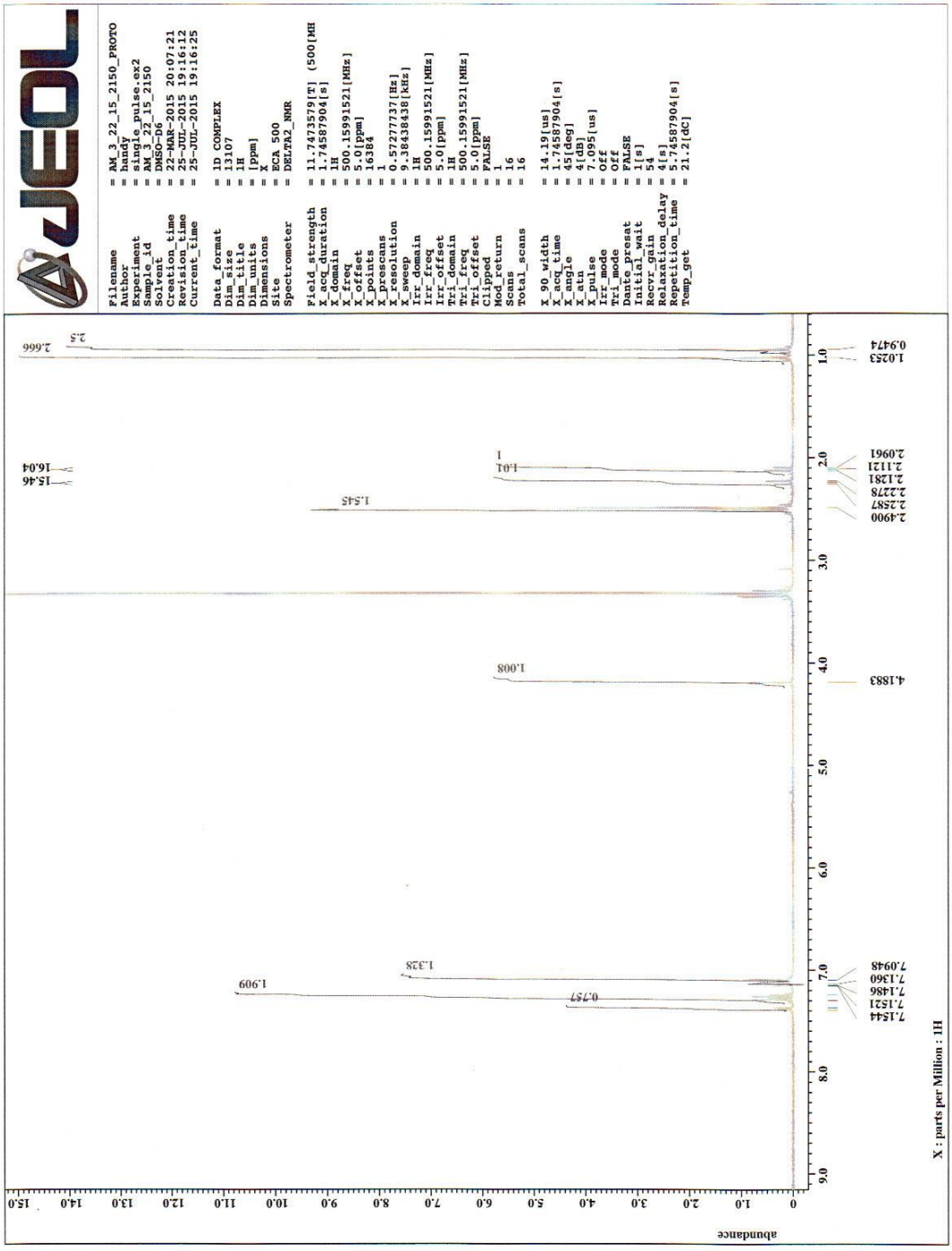

JEOL
Filename = AM_2140_1_PROTON-5.jd
Author = hamdi
Experiment = single_pulse.ex2
Sample_id = AM_2140_1
Solvent = DMSO-D6
Creation_time = 3-AUG-2015 01:26:33
Revision_time = 3-AUG-2015 01:47:30
Current_time = 3-AUG-2015 01:48:00
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.7473579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Date_Postesat = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 22.3[dC]
9.122
8.59
8.02
5.884
5.15
16.04
16.04
1.888
1.349
1.345
0.941
1.034
1.021
7.4773
7.4687
7.4601
7.1051
7.0891
7.0570
4.3647
4.3595
4.3429
4.1643
2.4934
2.2518
2.2358
2.2197
2.1052
2.0892
2.0732
1.0207
0.9337
abundance
X : parts per Million : 1H

2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

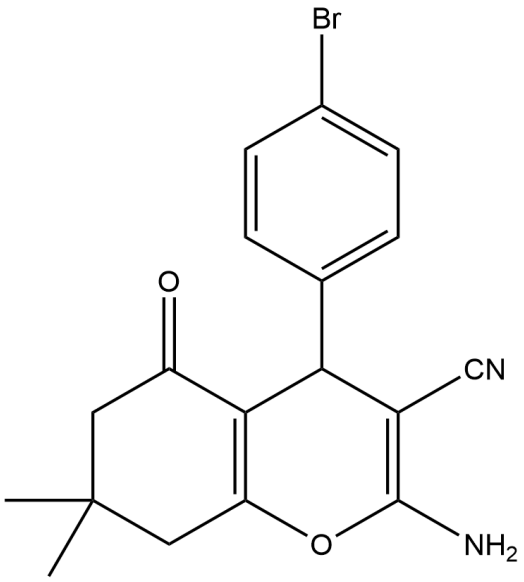


NMR

^{1}H NMR

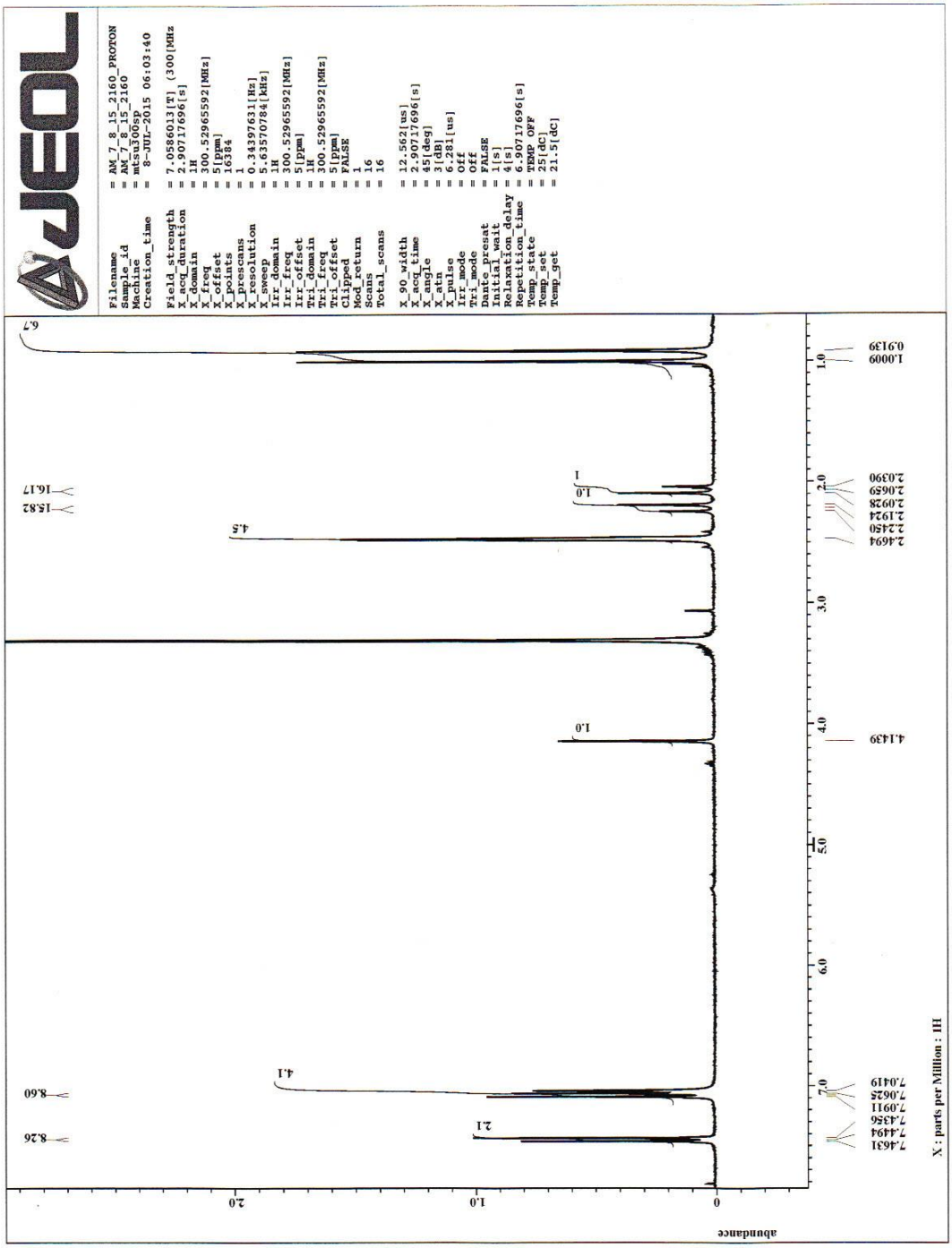

JEOL
Filename = AM_3_22_15_2150_PROTO
Author = Andy
Experiment = single_pulse.ex2
Sample_id = AM_3_22_15_2150
Solvent = DMSO-D6
Creation_time = 22-MAR-2015 20:07:21
Revision_time = 25-JUL-2015 19:16:12
Current_time = 25-JUL-2015 19:16:25
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735791[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Decoupler_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 54
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 21.2[dC]
2.666
2.5
16.04
15.46
1.545
1.01
1
1.008
1.328
1.909
0.757
0.9474
1.0253
2.0961
2.1121
2.1281
2.2278
2.2587
2.4900
4.1883
7.0948
7.1360
7.1486
7.1521
7.1544
abundance
X : parts per Million : 1H

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

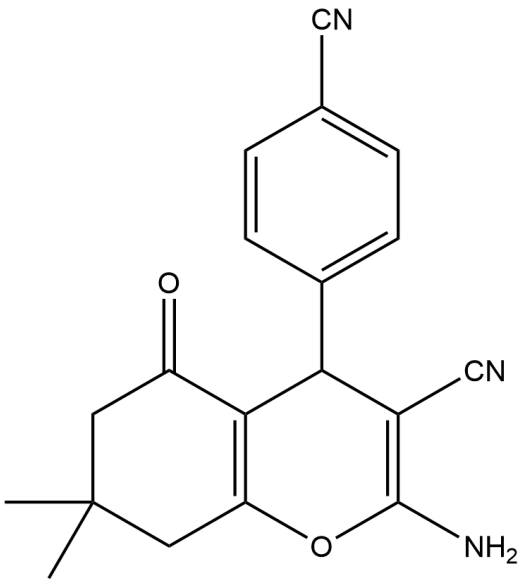


NMR

^{1}H NMR

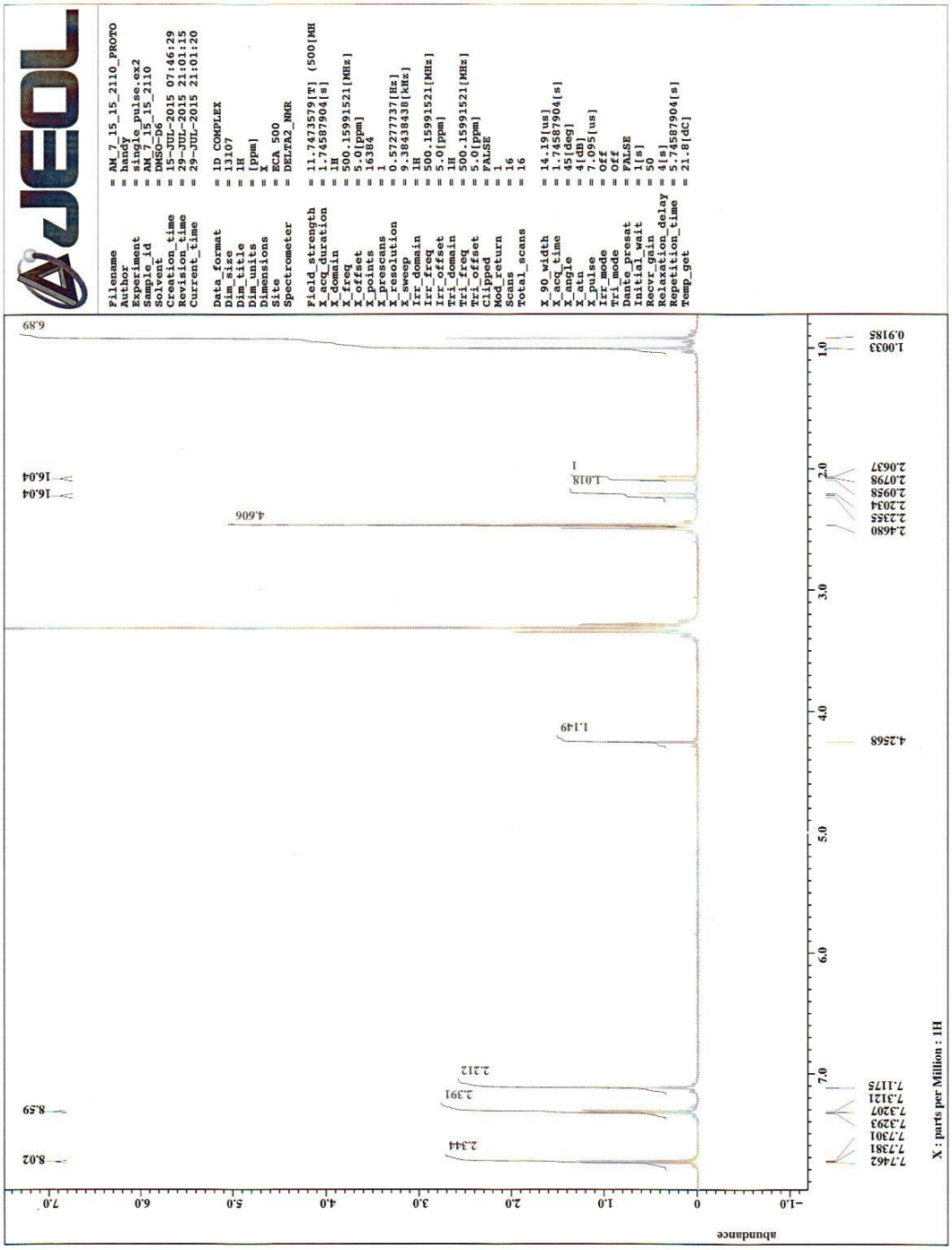

JEOL
Filename = AM_7_8_15_2160_PROTON
Sample_id = AM_7_8_15_2160
Solvent = mestd500sp
Creation_time = 8-JUL-2015 06:03:40
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 12.562[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.281[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Relaxation_delay = 4[s]
Repetition_time = 6.90717696[s]
Temp_state = TEMP OFF
Temp_set = 25[dC]
Temp_get = 21.5[dC]
6.7
16.17
15.82
4.5
1.0
1
8.60
8.26
4.1
2.1
1.0
abundance
0
1.0
2.0
0.9139
1.0009
2.4694
2.2450
2.1924
2.0928
2.0659
2.0390
4.1439
7.4631
7.4494
7.4356
7.0911
7.0625
7.0419
X : parts per Million : 1H

2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

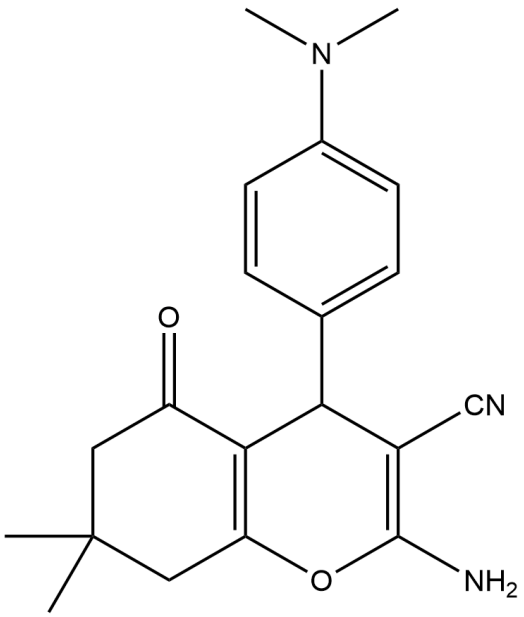


NMR

^{1}H NMR

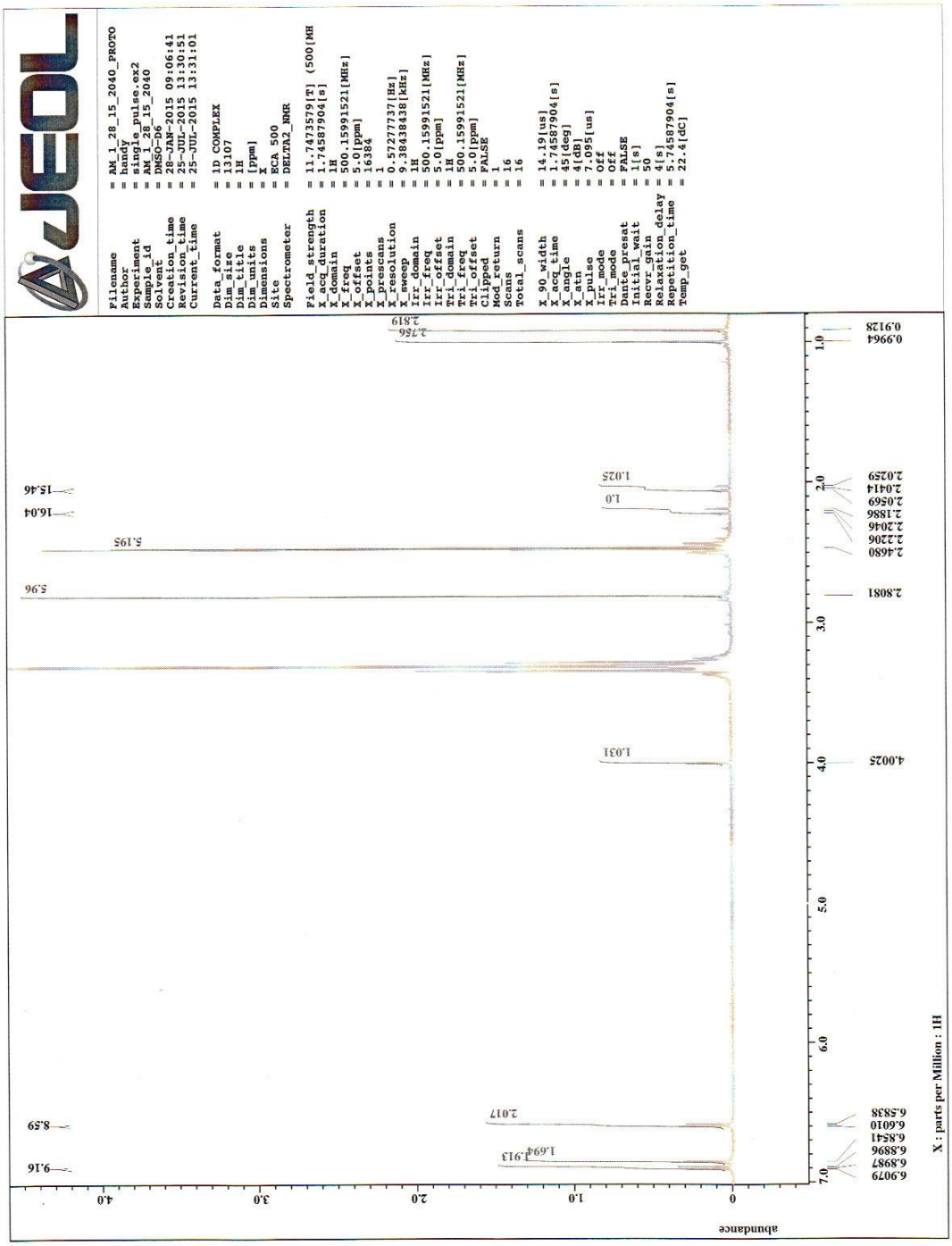

JEOL
Filename = AM_7_15_2110_PROTO
Author = hardy
Experiment = single_pulse.ex2
Sample_id = AM_7_15_2110
Solvent = DMSO-D6
Creation_time = 15-JUL-2015 07:46:29
Revision_time = 29-JUL-2015 21:01:15
Current_time = 29-JUL-2015 21:01:20
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = RCA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.7473579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 21.8[dC]
6.89
16.04
16.04
4.606
1.018
1
1.149
2.212
2.391
2.344
8.59
8.02
7.7462
7.7381
7.7301
7.3293
7.3207
7.3121
7.1175
4.2568
2.4680
2.2355
2.2034
2.0958
2.0798
2.0637
1.0033
0.9185
abundance
X : parts per Million : 1H

2-Amino-4-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

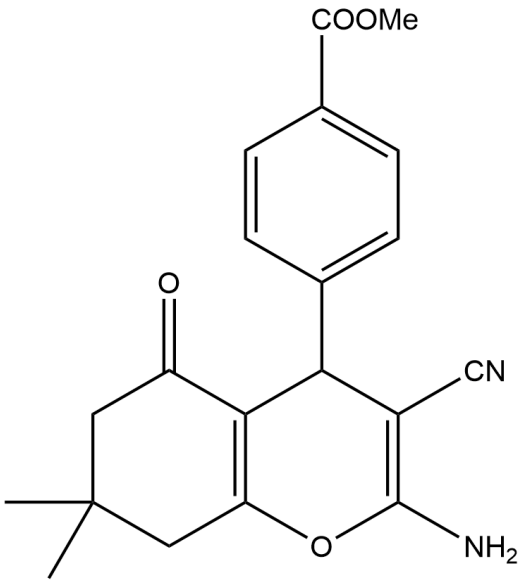


NMR

^{1}H NMR

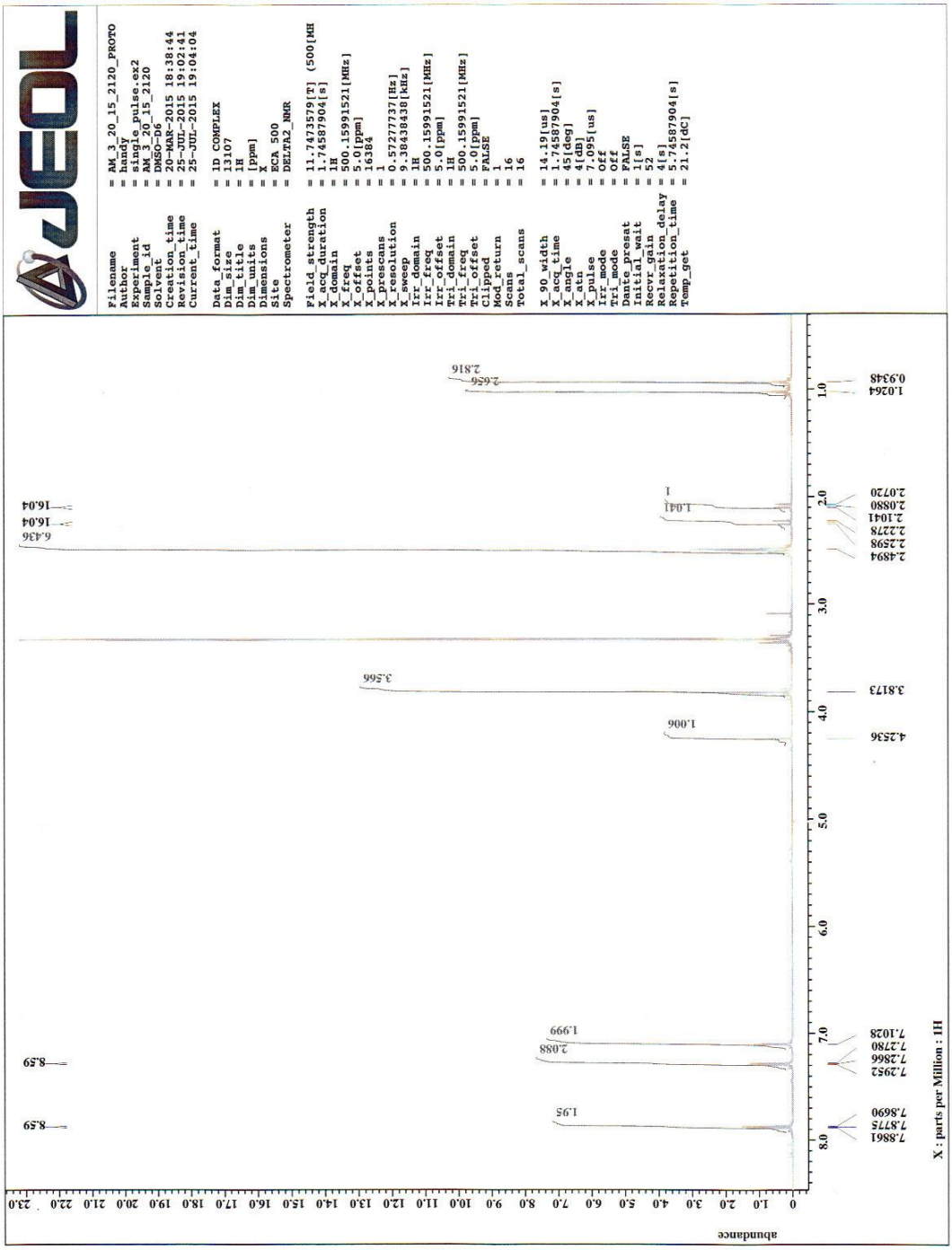

JEOL
Filename = AM_1_28_15_2040_PROTO
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_1_28_15_2040
Solvent = DMSO-D6
Creation_time = 28-JAN-2015 09:06:41
Revision_time = 25-JUL-2015 13:30:51
Current_time = 25-JUL-2015 13:31:01
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.7473579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 22.4[dC]
2.819
2.756
1.025
1.0
15.46
16.04
5.195
5.96
1.031
2.017
1.694
1.913
9.16
8.59
0.9128
0.9964
2.0259
2.0414
2.0569
2.1886
2.2046
2.2206
2.4680
2.8081
4.0025
6.5838
6.6010
6.8541
6.8896
6.8987
6.9079
abundance
X : parts per Million : 1H

2-Amino-4-(4-carboxymethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

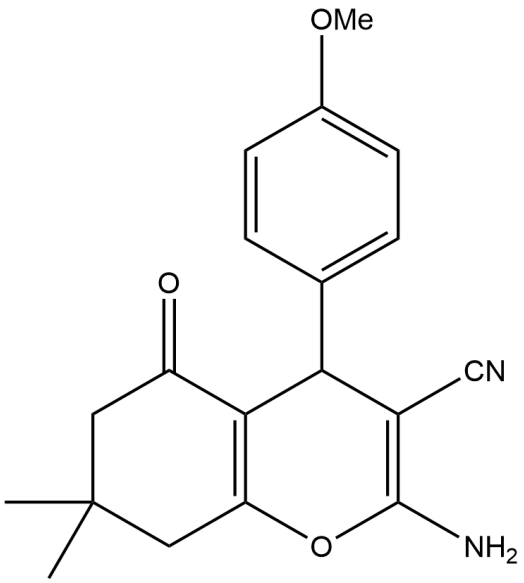


NMR

^{1}H NMR

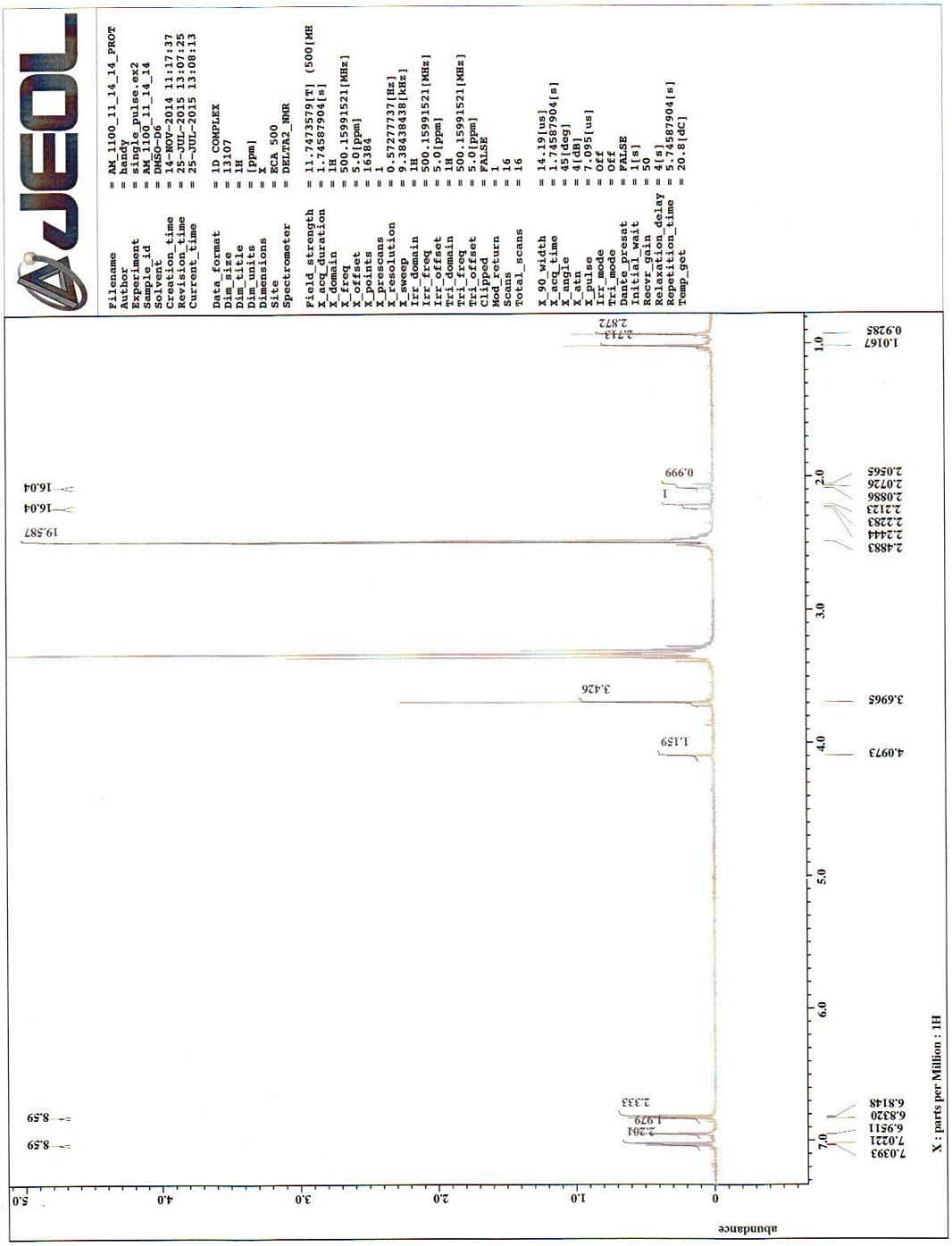

JEOL
Filename = AM_3_20_15_2120_PROTO
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_3_20_15_2120
Solvent = DMSO-D6
Creation_time = 20-MAR-2015 18:38:44
Revision_time = 25-JUL-2015 19:02:41
Current_time = 25-JUL-2015 19:04:04
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = 1
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.7473579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
X_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Irr_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 52
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 21.2[dC]
2.816
2.656
1.041
1
3.566
1.006
1.999
2.088
1.95
6.436
16.04
16.04
8.59
8.59
0.9348
1.0264
2.0720
2.0880
2.1041
2.2278
2.2598
2.4894
3.8173
4.2536
7.8861
7.8775
7.8690
7.2952
7.2866
7.2780
7.1028
abundance
X : parts per Million : 1H

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

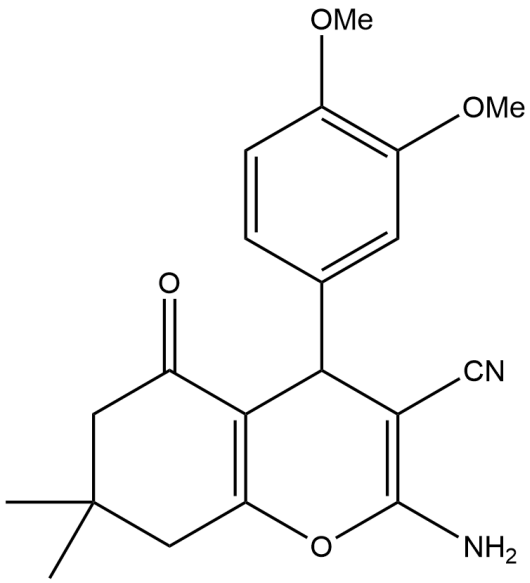


NMR

^{1}H NMR

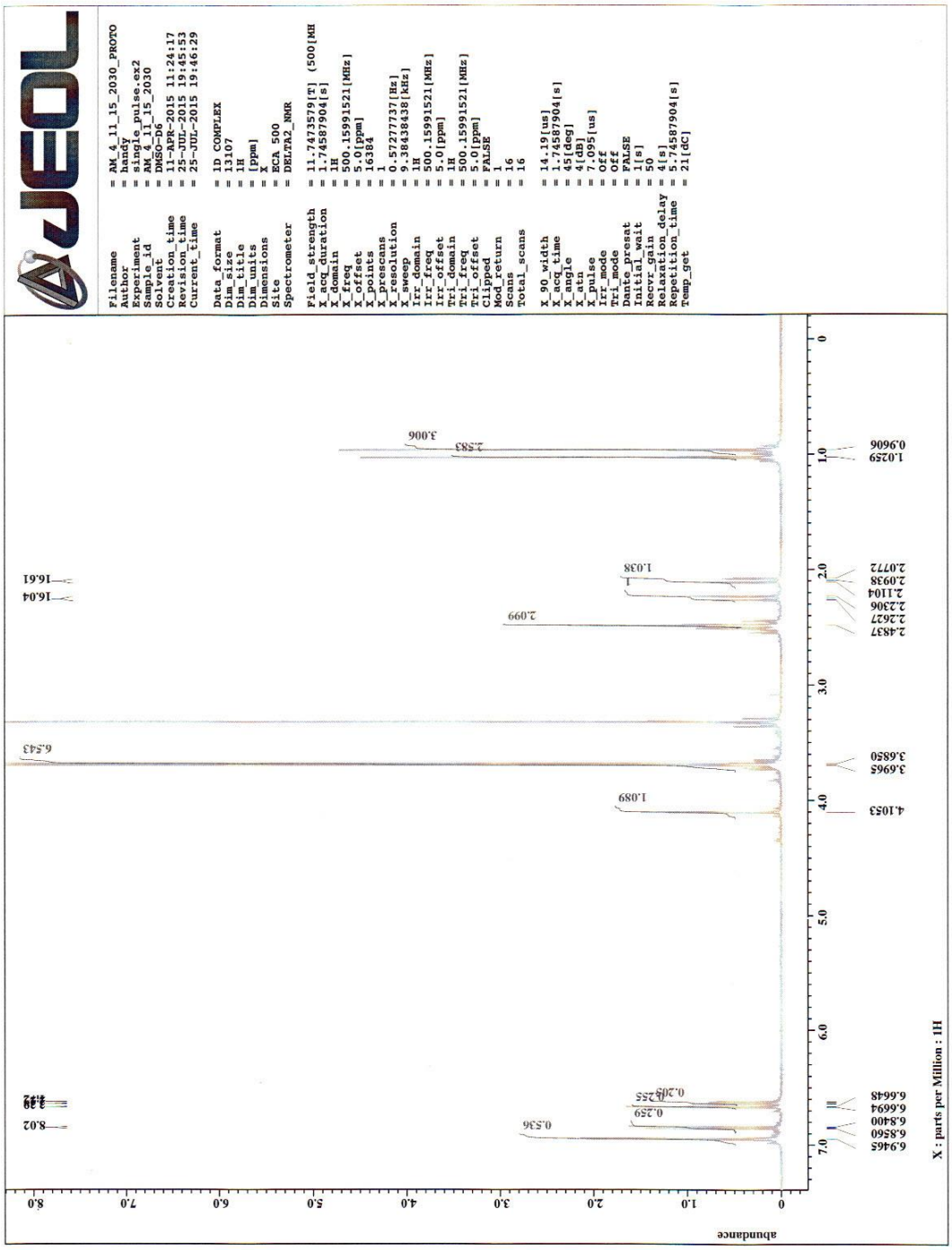

JEOL
Filename = AM_1100_11_14_14_PROT
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_1100_11_14_14
Solvent = DMSO-D6
Creation_time = 14-NOV-2014 11:17:37
Revision_time = 25-JUL-2015 13:07:25
Current_time = 25-JUL-2015 13:08:13
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.159991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 0
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.159991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.159991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 20.8[dC]
abundance
X : parts per Million : 1H
8.59
8.59
16.04
16.04
19.587
2.333
2.304
1.979
6.8148
6.8320
6.9511
7.0221
7.0393
3.426
1.159
2.872
2.713
0.999
1
4.0973
3.6965
2.4883
2.2444
2.2283
2.2123
2.0886
2.0726
2.0565
1.0167
0.9285

2-Amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

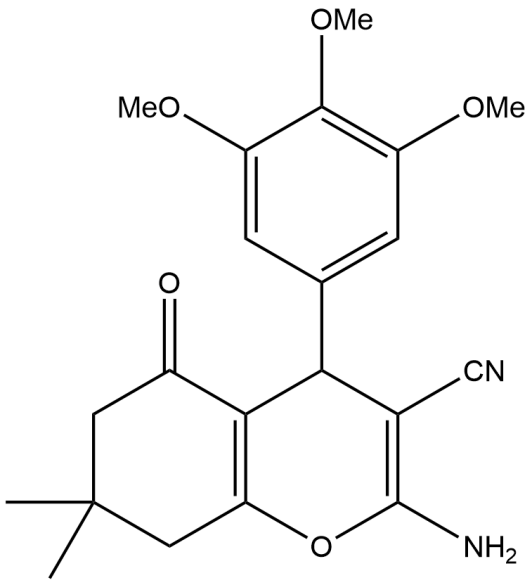


NMR

^{1}H NMR

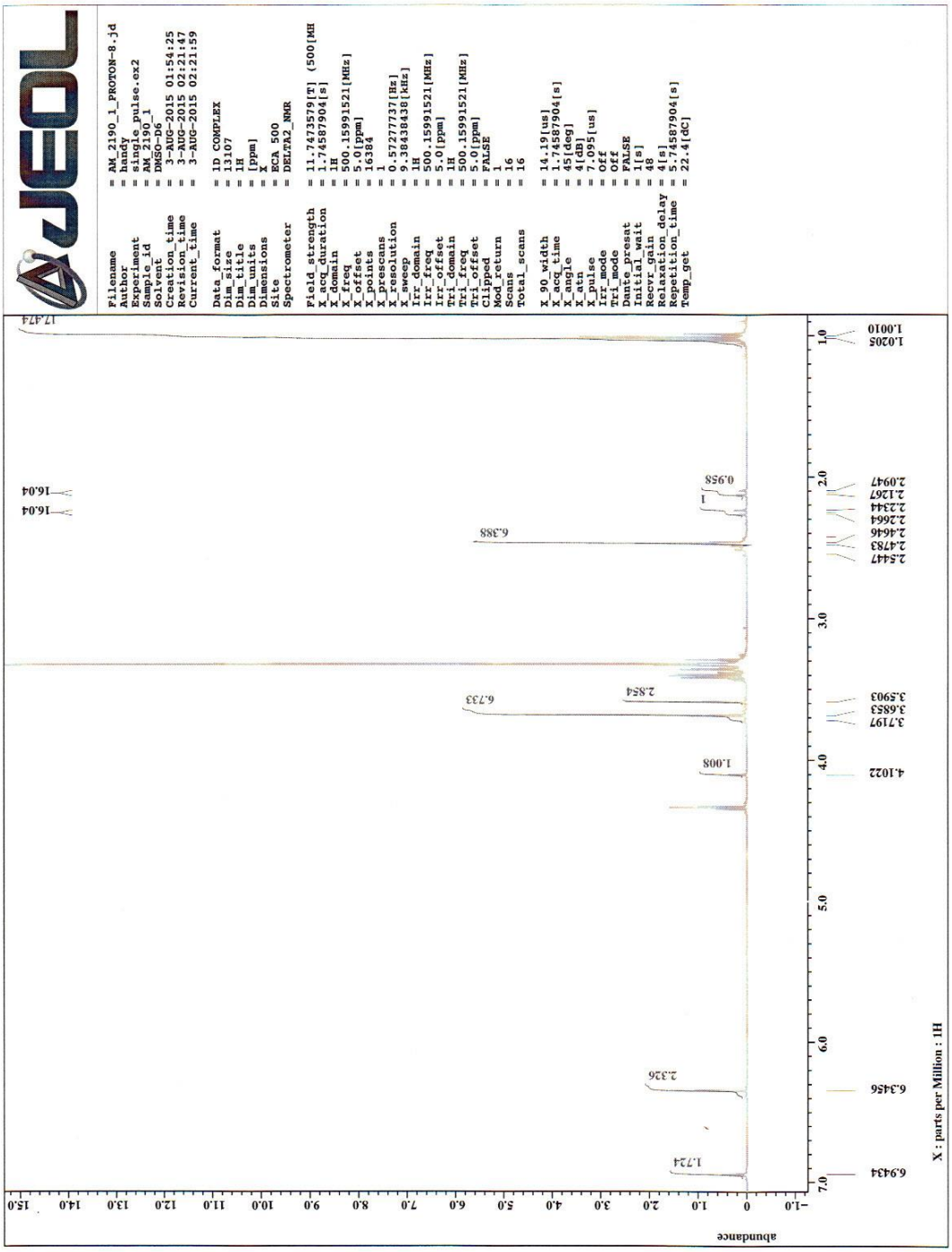

JEOL
Filename = AM_4_11_15_2030_PROTO
Author = hanagy
Experiment = single_pulse.ex2
Sample_id = AM_4_11_15_2030
Solvent = DMSO-D6
Creation_time = 11-APR-2015 11:24:17
Revision_time = 25-JUL-2015 19:45:53
Current_time = 25-JUL-2015 19:46:29
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735791[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = FALSE
Decpl_mesat = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 21[dC]
abundance
X : parts per Million : 1H
8.02
3.99
3.92
16.61
16.04
6.543
6.9465
6.8560
6.8400
6.6694
6.6648
0.536
0.259
0.2255
3.006
2.583
2.099
1.089
1.038
4.1053
3.6965
3.6850
2.4837
2.2627
2.2306
2.1104
2.0938
2.0772
1.0259
0.9606

2-Amino-4-(3,4,5-trimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

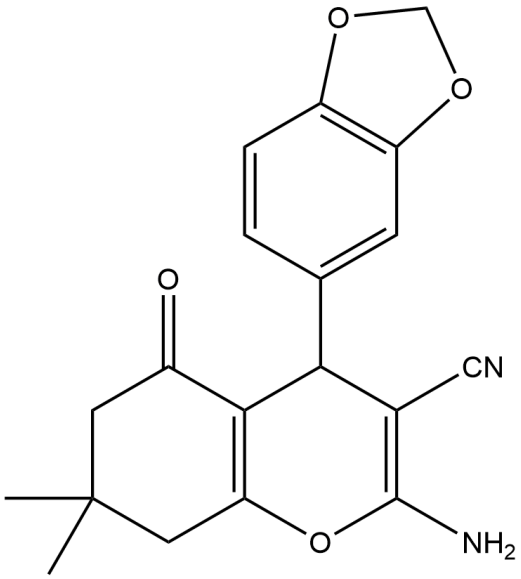


NMR

^{1}H NMR

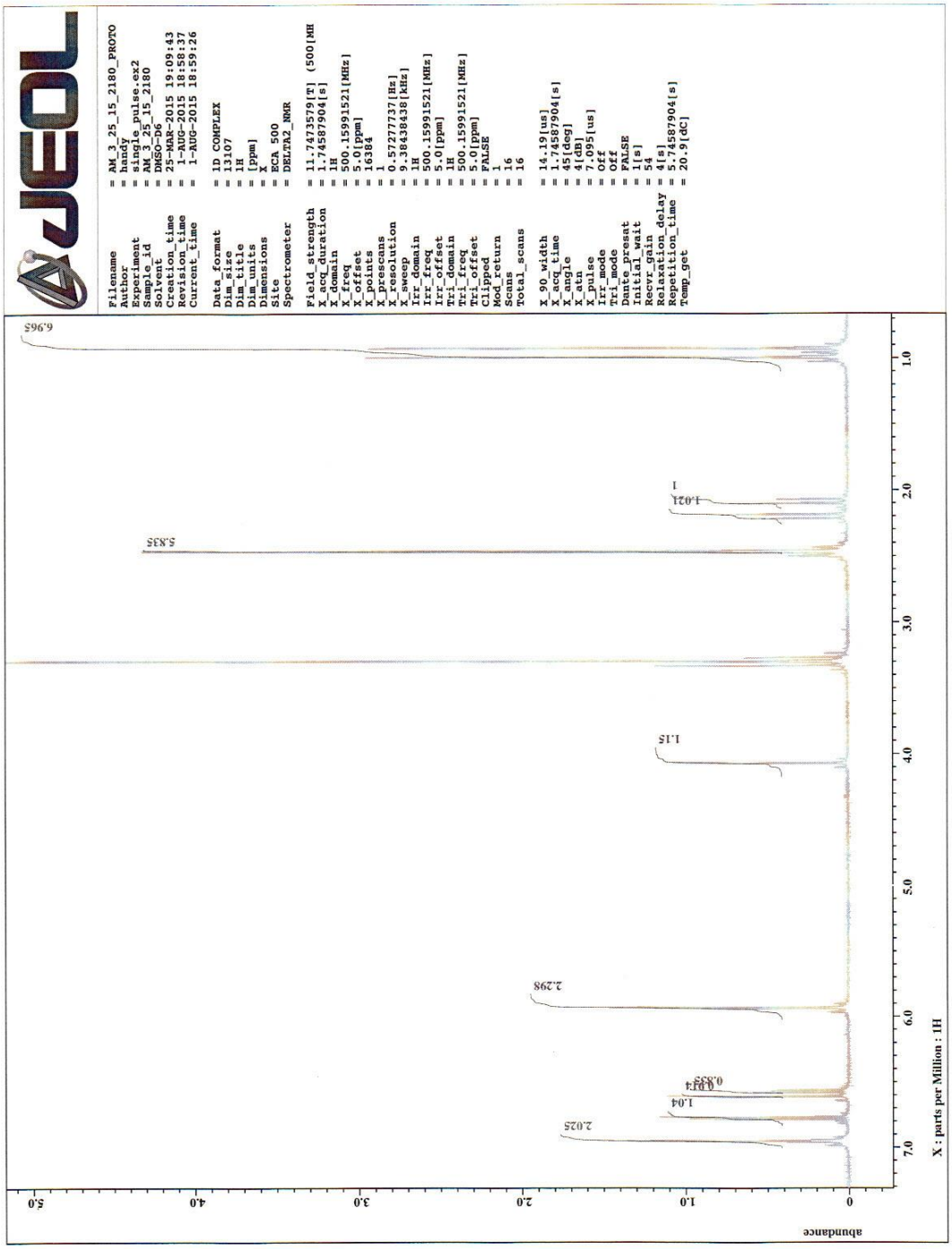

JEOL
Filename = AM_2190_1_PROTON-8.jd
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_2190_1
Solvent = DMSO-D6
Creation_time = 3-AUG-2015 01:54:25
Revision_time = 3-AUG-2015 02:21:47
Current_time = 3-AUG-2015 02:21:59
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = RCA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 4.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 48
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 22.4[dC]
17.474
16.04
16.04
0.958
1
6.388
6.733
2.854
1.008
2.326
1.724
1.0205
1.0010
2.5447
2.4783
2.4646
2.2664
2.2344
2.1267
2.0947
3.5903
3.6853
3.7197
4.1022
6.3456
6.9434
abundance
X : parts per Million : 1H

2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

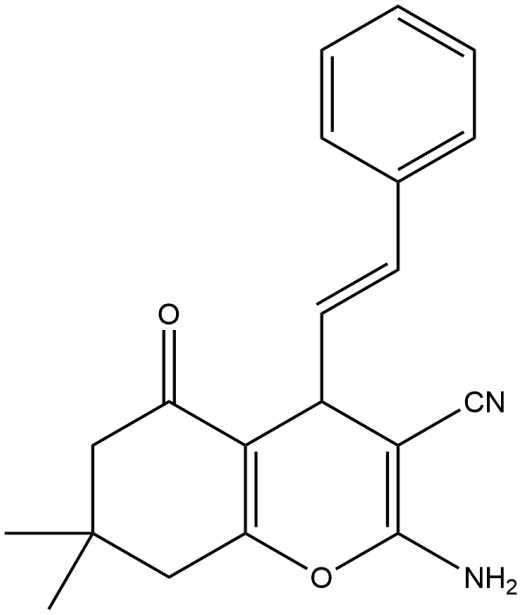


NMR

^{1}H NMR

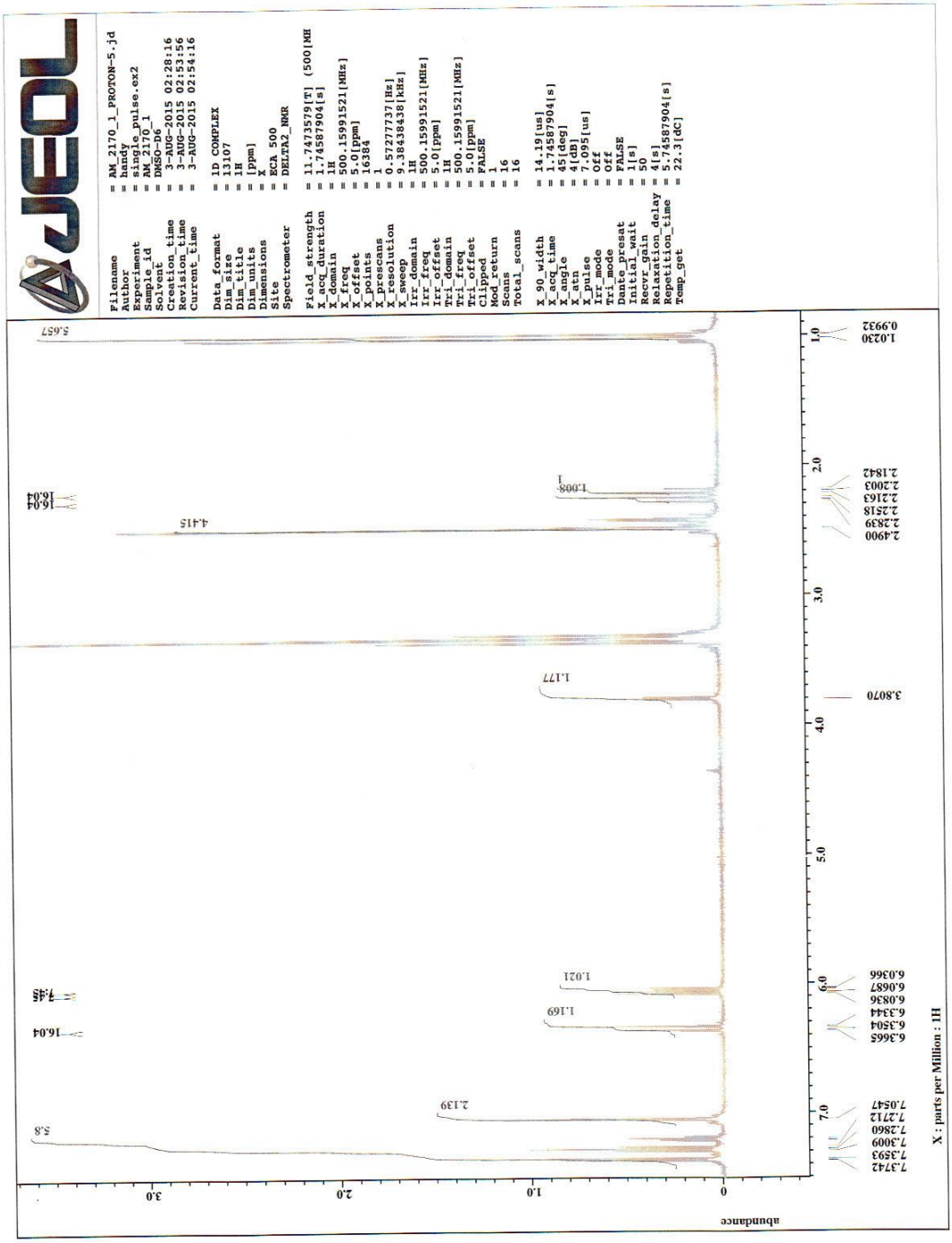

JEOL
Filename = AM_3_25_15_2180_PROTO
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_3_25_15_2180
Solvent = DMSO-D6
Creation_time = 25-MAR-2015 19:09:43
Revision_time = 1-AUG-2015 18:58:37
Current_time = 1-AUG-2015 18:59:26
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735791[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.159991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.159991521[MHz]
Irr_offset = 11.0[ppm]
Tri_domain = 1H
Tri_freq = 500.159991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 54
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 20.9[dC]
6.965
5.835
1.021
1.15
2.298
0.834
1.04
2.025
abundance
X : parts per Million : 1H

2-Amino-4-(2-phenylethenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

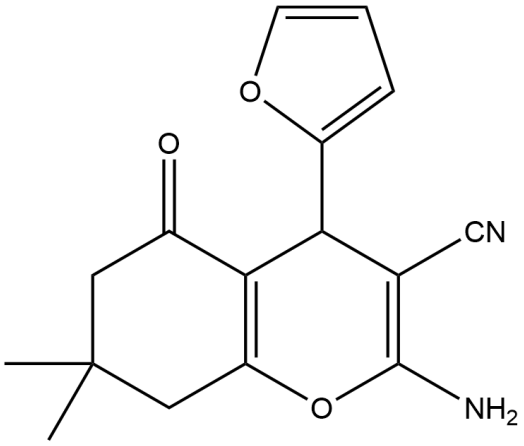


NMR

^{1}H NMR

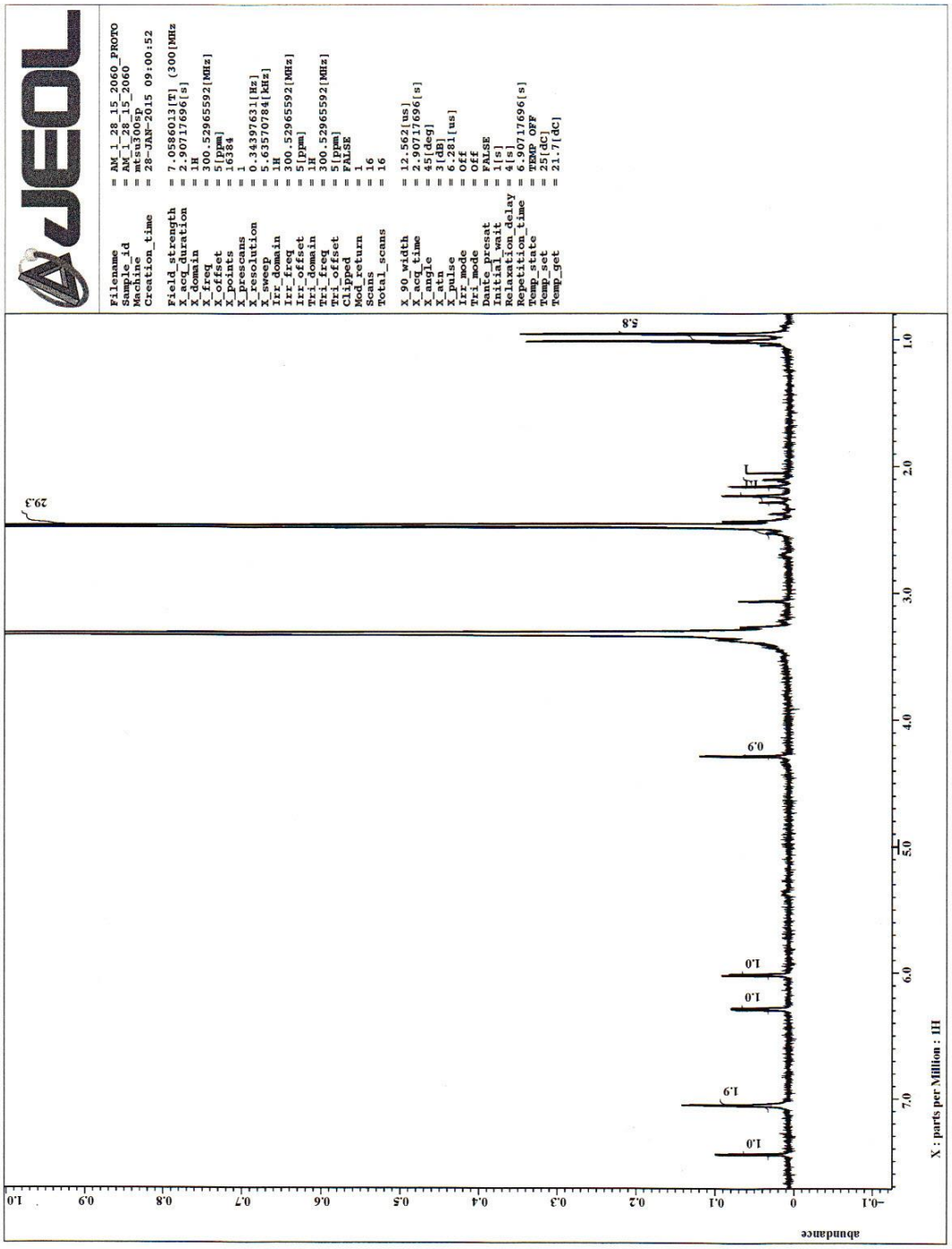

JEOL
Filename = AM_2170_1_PROTON-5.jid
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_2170_1
Solvent = DMSO-D6
Creation_time = 3-AUG-2015 02:28:16
Revision_time = 3-AUG-2015 02:53:56
Current_time = 3-AUG-2015 02:54:16
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.7473579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.159991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.57277737[Hz]
X_sweep = 9.38438438[kHz]
Irr_domain = 1H
Irr_freq = 500.159991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.159991521[MHz]
Tri_offset = 5.0[ppm]
Clip_mod = FALSE
Mod_preturn = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Repetition = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 22.3[dC]
5.657
16.04
4.415
1.008
1.177
3.8070
1.021
1.169
7.45
16.04
2.139
5.8
0.9932
1.0230
2.1842
2.2003
2.2163
2.2518
2.2839
2.4900
6.3665
6.3504
6.3344
6.0836
6.0687
6.0366
7.3742
7.3593
7.3009
7.2860
7.2712
7.0547
abundance
X : parts per Million : 1H

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

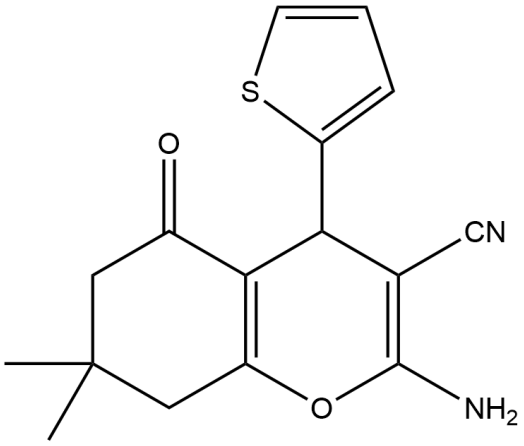


NMR

^{1}H NMR

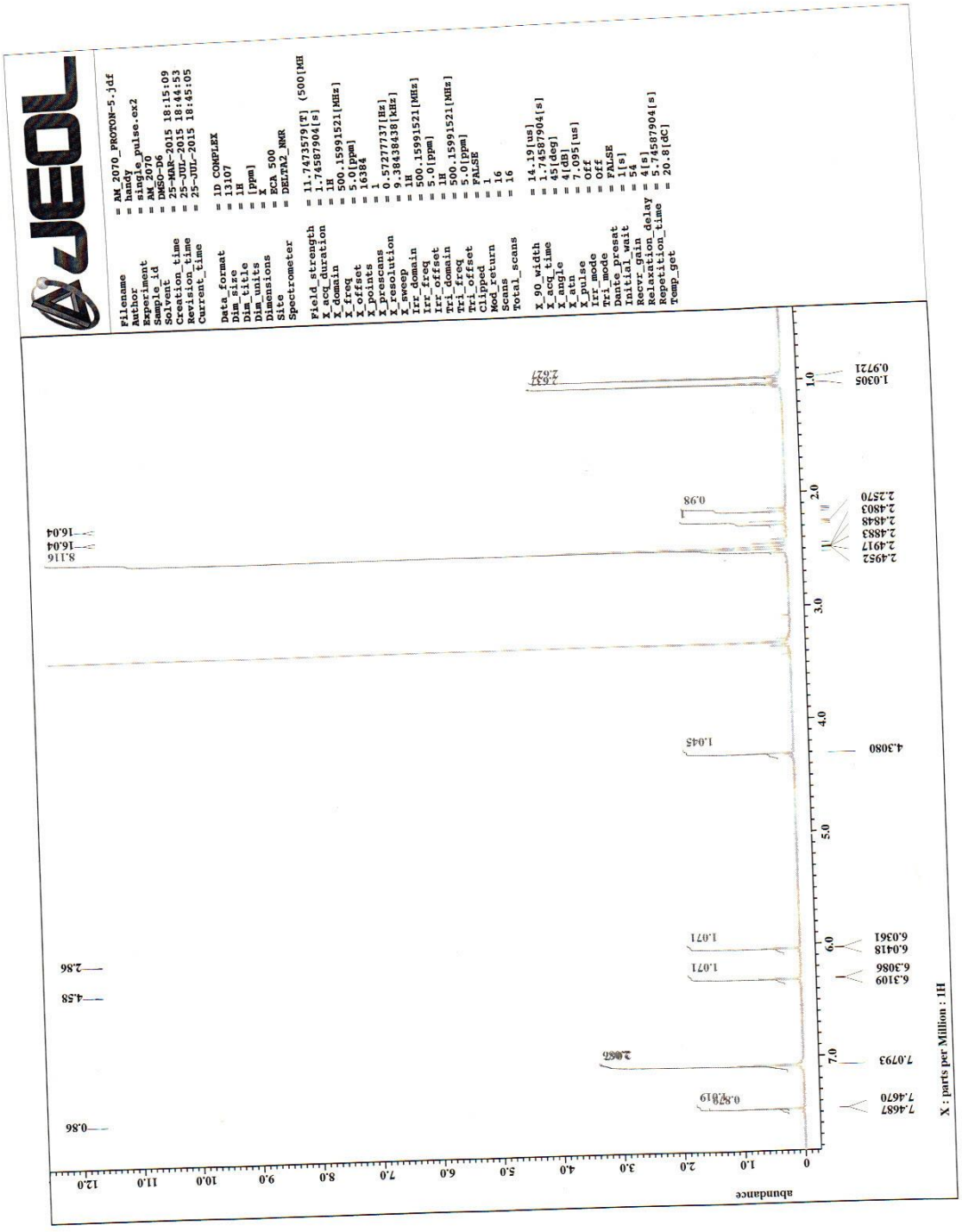

JEOL
Filename = AM_1_28_15_2060_PROTO
Sample_id = AM_1_28_15_2060
Machine = mtsu300sp
Creation_time = 28-JAN-2015 09:00:52
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 12.562[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.281[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Relaxation_delay = 4[s]
Repetition_time = 6.90717696[s]
Temp_state = TEMP OFF
Temp_set = 25[dC]
Temp_get = 21.7[dC]
29.3
5.8
1.0
1.9
1.0
1.0
0.9
abundance
X : parts per Million : 1H

2-Amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

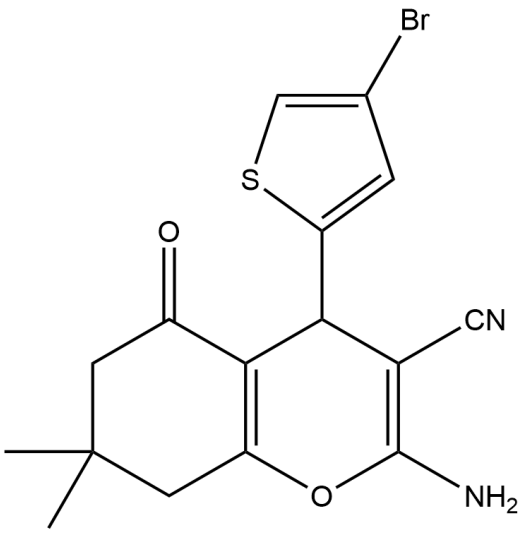


NMR

^{1}H NMR


JEOL
Filename = AM_2070_PROTON-5.jdf
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_2070
Solvent = DMSO-D6
Creation_time = 25-MAR-2015 18:15:09
Revision_time = 25-JUL-2015 18:44:53
Current_time = 25-JUL-2015 18:45:05
1D COMPLEX
Data_format = 13107
Dim_size = 1H
Dim_title = [ppm]
Dim_units = X
Dimensions = ECA 500
Site = DELTA2_NMR
Spectrometer = 11.74735791[T] (500[MH
Field_strength = 1.74587904[s]
X_acq_duration = 1H
X_domain = 500.15991521[MHz]
X_freq = 5.0[ppm]
X_offset = 16384
X_points = 1
X_prescans = 0.57277737[Hz]
X_resolution = 9.384384381[kHz]
X_sweep = 1H
Irr_domain = 500.15991521[MHz]
Irr_freq = 5.0[ppm]
Irr_offset = 1H
Tri_domain = 500.15991521[MHz]
Tri_freq = 5.0[ppm]
Tri_offset = FALSE
Clip_ped = 1
Mod_peturn = 16
Scans = 16
Total_scans = 14.19[us]
X_90_width = 1.74587904[s]
X_acq_time = 45[deg]
X_angle = 4[dB]
X_atn = 7.095[us]
X_pulse = Off
Irr_mode = Off
Tri_mode = FALSE
Dante_Presat = 1[s]
Initial_wait = 54
Receiver_gain = 4[s]
Relaxation_delay = 5.74587904[s]
Repetition_time = 20.8[dC]
Temp_get
2.627
0.98
1.045
1.071
1.071
2.068
0.829
0.819
16.04
16.04
8.116
2.86
4.58
0.86
1.0305
0.9721
2.2570
2.4803
2.4848
2.4883
2.4917
2.4952
4.3080
6.0418
6.0361
6.3109
6.3086
7.0793
7.4687
7.4670
abundance
X : parts per Million : 1H

2-Amino-7,7-dimethyl-5-oxo-4-(4-bromothiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile



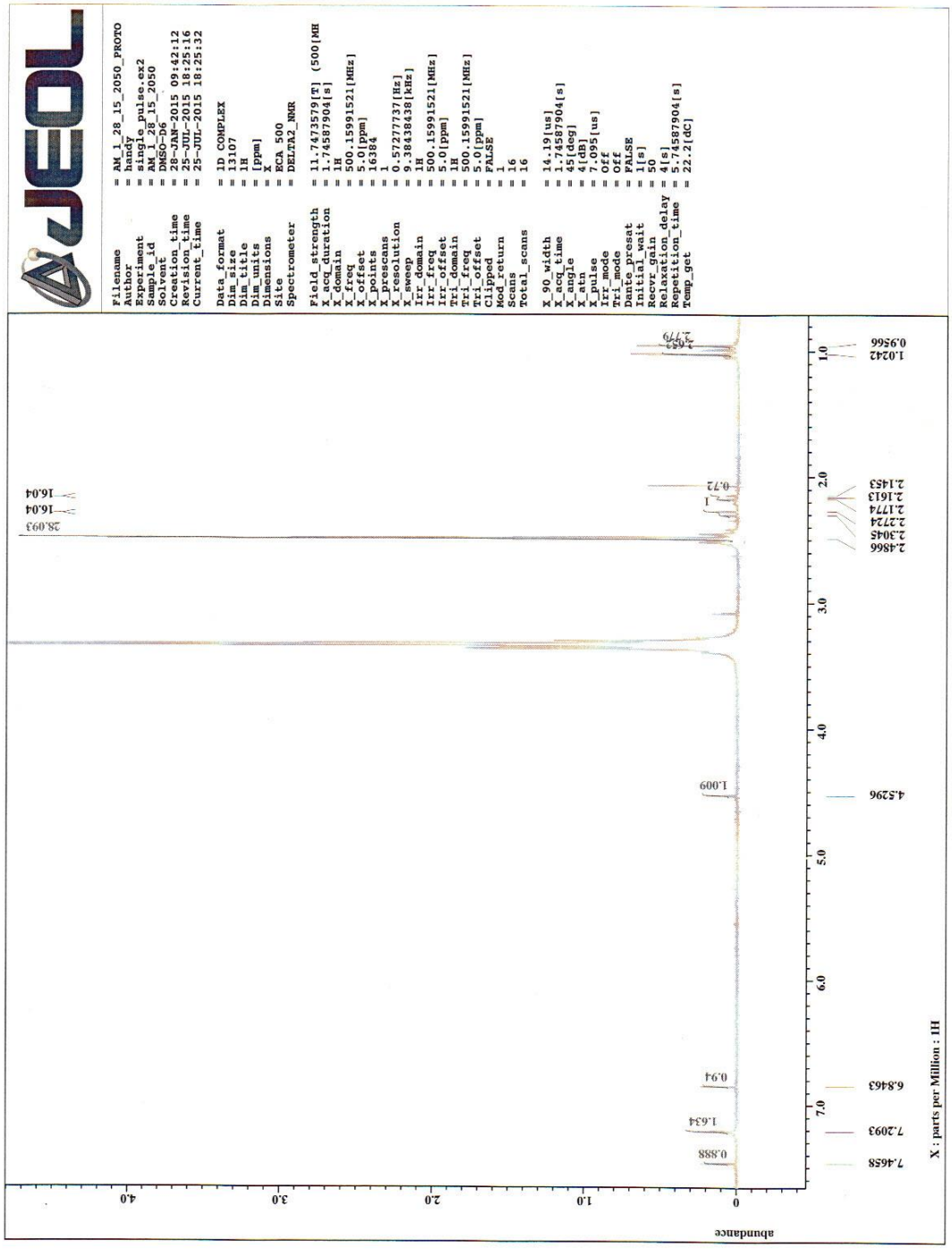
NMR

^{1}H NMR

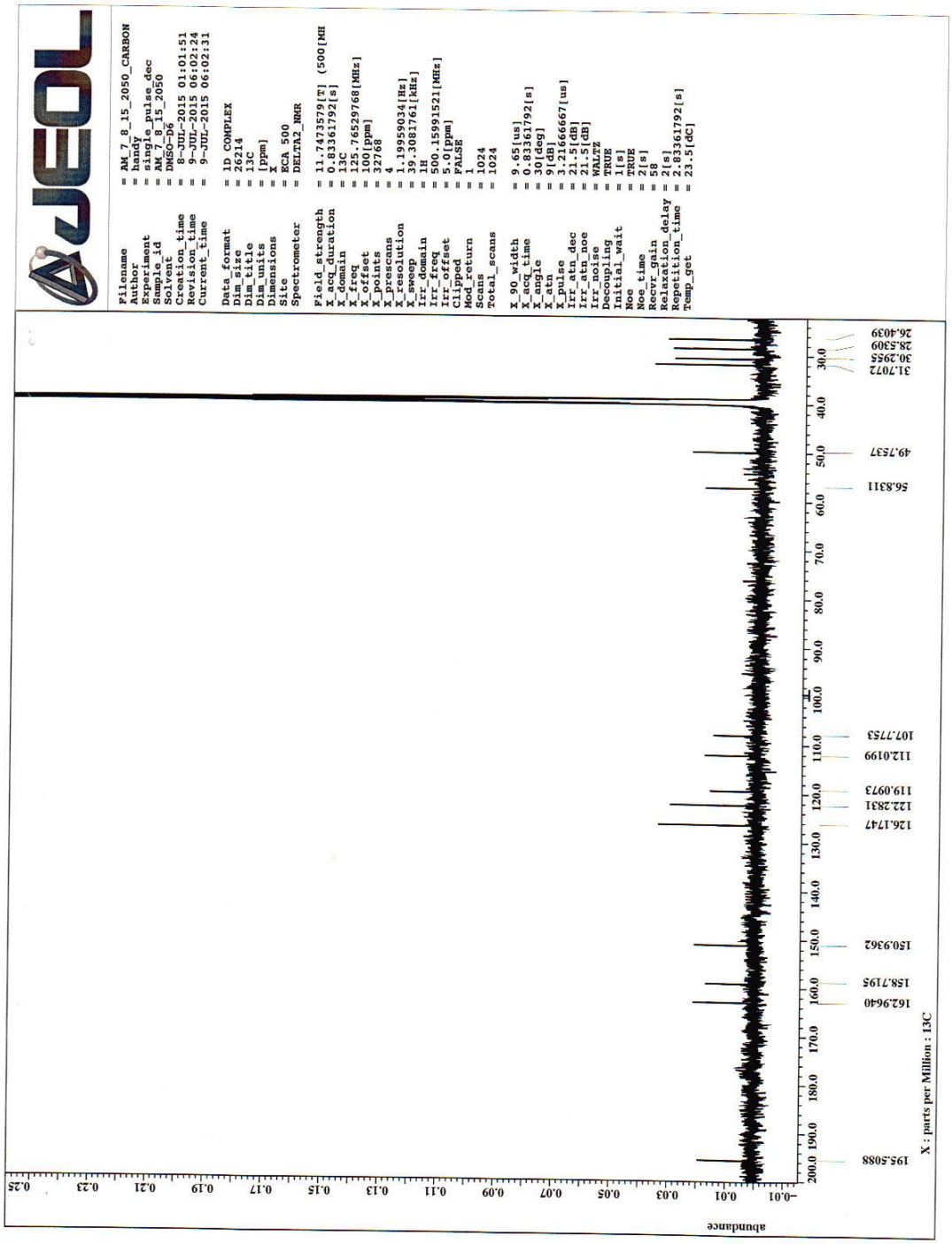
^{13}C NMR

FTIR

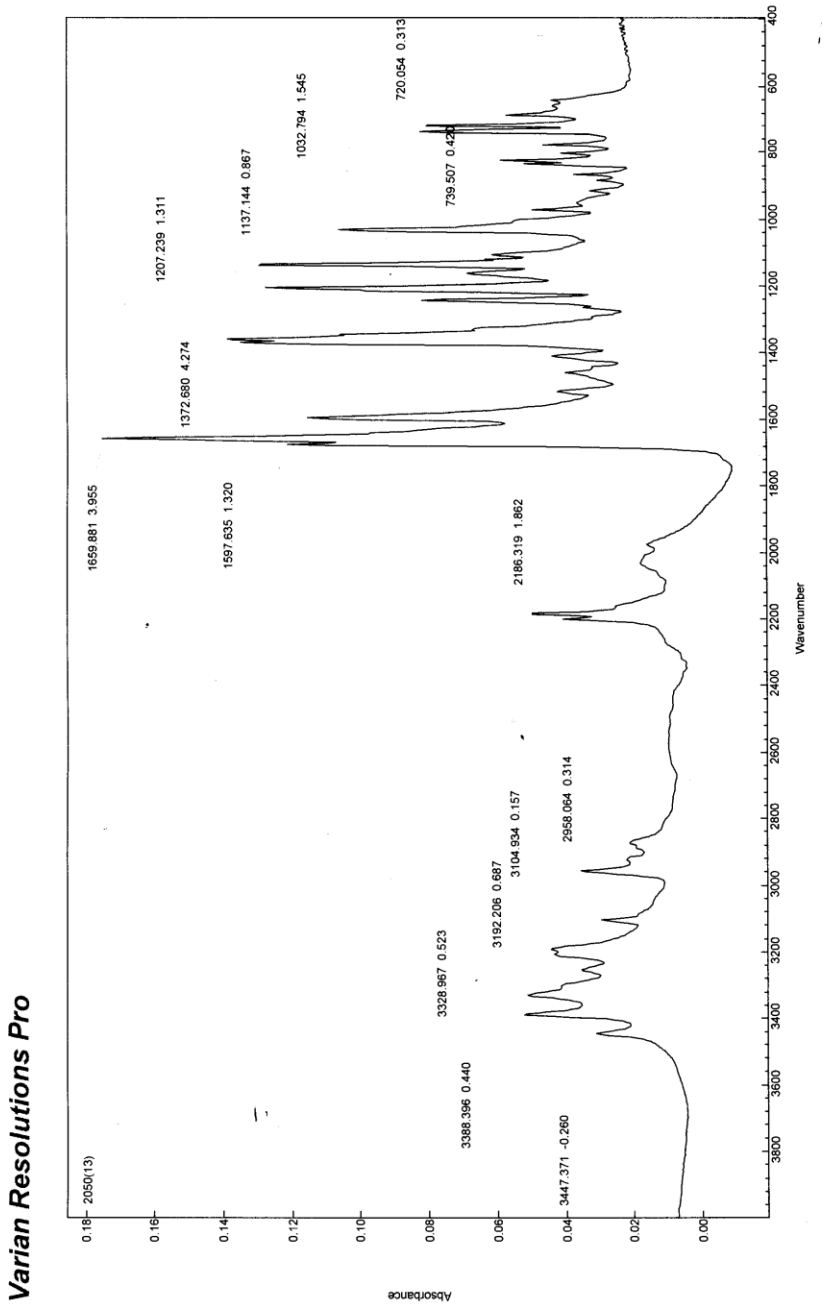
^{1}H NMR


JEOL
Filename = AM_1_28_15_2050_PROTO
Author = handy
Experiment = single_pulse.ex2
Sample_id = AM_1_28_15_2050
Solvent = DMSO-D6
Creation_time = 28-JAN-2015 09:42:12
Revision_time = 25-JUL-2015 18:25:16
Current_time = 25-JUL-2015 18:25:32
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.7473579[T] (500[MH
X_acq_duration = 1.74587904[s]
X_domain = 1H
X_freq = 500.15991521[MHz]
X_offset = 5.0[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 9.57277737[Hz]
X_sweep = 9.38436438[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Tri_domain = 1H
Tri_freq = 500.15991521[MHz]
Tri_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 16
Total_scans = 16
X_90_width = 14.19[us]
X_acq_time = 1.74587904[s]
X_angle = 45.0[deg]
X_atn = 4[dB]
X_pulse = 7.095[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 50
Relaxation_delay = 4[s]
Repetition_time = 5.74587904[s]
Temp_get = 22.2[dC]
16.04
16.04
28.093
0.72
1
1.009
0.94
1.634
0.888
7.4658
7.2093
6.8463
4.5296
2.4866
2.3045
2.2724
2.1774
2.1613
2.1453
1.0242
0.9566
abundance
X : parts per Million : 1H

^{13}C NMR


JEOL
Filename = AM_7_8_15_2050_CARBON
Author = handy
Experiment = single_pulse_dec
Sample_id = AM_7_8_15_2050
Solvent = DMSO-D6
Creation_time = 9-JUL-2015 01:01:51
Revision_time = 9-JUL-2015 06:02:24
Current_time = 9-JUL-2015 06:02:31
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECA 500
Spectrometer = DELTA2_NMR
Field_strength = 11.74735791[T] (500[MH
X_acq_duration = 0.83361792[s]
X_domain = 13C
X_freq = 125.76529768[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 1.19959034[Hz]
X_sweep = 39.30817761[kHz]
Irr_domain = 1H
Irr_freq = 500.15991521[MHz]
Irr_offset = 5.0[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 1024
Total_scans = 1024
X_90_width = 9.65[us]
X_acq_time = 0.83361792[s]
X_angle = 30[deg]
X_atn = 9[dB]
X_pulse = 3.21666667[us]
Irr_atn_dec = 21.5[dB]
Irr_atn_noe = 21.5[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Relaxation_delay = 58
Recvr_gain = 21[s]
Repetition_time = 2.83361792[s]
Temp_get = 23.5[dC]
26.4039
28.5309
30.2955
31.7072
49.7537
56.8311
107.7753
112.0199
119.0973
122.2831
126.1747
150.9362
158.7195
162.9640
195.5088
X : parts per Million : 13C
abundance

FTIR


Varian Resolutions Pro
2050(13)
1659.881 3.955
1597.635 1.320
1372.680 4.274
1207.239 1.311
1137.144 0.867
1032.794 1.545
739.507 0.420
720.054 0.313
2186.319 1.862
3328.967 0.523
3388.396 0.440
3192.206 0.687
3104.934 0.157
2958.064 0.314
3447.371 -0.260
Absorbance
Wavenumber