Synthesis and Characterization of Pyridine and Pyrimidine Derivatives

Project report submitted to the Central University of Punjab

For the award of

Master of Science

Chemical Sciences (Medicinal Chemistry)

In

Department of Pharmaceutical Sciences and Natural Products

By

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Supervisor

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School of Basic and Applied Sciences

Central University of Punjab, Bathinda

June, 2018

DECLARATION

I declare that the project report entitled "**Synthesis and characterization of pyridine and pyrimidine derivatives**" has been prepared by me under the guidance of Dr. Kaki Venkata Rao, Assistant Professor, Department of Pharmaceutical Sciences and Natural Products, School of Basic and Applied Sciences, Central University of Punjab. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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Date:

CERTIFICATE

I certified that Desoshree Ghosh has prepared her project report entitled "**Synthesis and characterization of pyridine and pyrimidine derivatives**", for the award of M.Sc. Degree of the Central University of Punjab, under my guidance. She has carried out this work at the Department of Pharmaceutical Sciences and Natural Products, School of Basic and Applied Sciences, Central University of Punjab.

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Date:

ABSTRACT

"Synthesis and Characterization of Pyridine and Pyrimidine Derivatives"

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Degree for which submitted: M.Sc. Chemical Sciences (Medicinal Chemistry)

Name of Supervisor: Dr. Kaki Venkata Rao

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Key words: Pyridine, pyrimidine

Pyridine and pyrimidine derivatives are important chemical compounds with tremendous biological applications. Fusion of pyrimidine moiety with different heterocycle scaffolds gives rise to a new class of hybrid heterocycles possessing improved activity. In our project work, we synthesized pyridine derivatives (Nicotinonitrile) and thieno[2,3-*d*]pyrimidine derivatives which may be further explored to generate novel compounds with several biological activities.

(Desoshree Ghosh) (Dr. Kaki Venkata Rao)

ACKNOWLEDGEMENTS

I have taken efforts in this project. However, it would not have been possible without the kind support and help of many individuals and organization. I would like to extend my sincere thanks to all of them.

I would like to express my sincere thanks to **Prof. R.K.Kohli**, Vice Chancellor and **Prof. (Dr.) P. Ramarao**, Dean Academic affairs, Central University of Punjab for providing me direction and facilities to carry out my research work.

I am highly indebted to my guide **Dr. Kaki Venkata Rao**, Assistant professor, Department of Pharmaceutical Sciences and Natural Projects, Central University of Punjab, for his guidance and constant supervision as well as for providing necessary information regarding the projects and also for his support in completing the project.

I am pleased to extend my thanks to **Dr. Raj Kumar**, Associate Professor, **Dr. Vinod kumar**, **Dr. Vikas Jaitak** and **Dr. Pradeep Kumar**, Assistant Professor, Department of Pharmaceutical Sciences and Natural Products for their support and guidance through all these years.

I feel proud to say that due to keen knowledge of my seniors, it was quite easy for me to learn lot of knowledge about research and to complete of my dissertation work on time.

I would like to express my gratitude towards my parents for their kind cooperation and encouragement.

I would like to express the deepest appreciation to my friends Prati (cuty), Gourab and Bittu for their constant help and support.

Last but not the least I am very thankful to **Mr. Rajesh Tiwari**, Junior Technical Assistant for his help in the lab

Desoshree Ghosh

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LIST OF ABBREVIATION

Sr. No	Full form	Abbreviation
1	Room temperature	rt
2	Celcius	C
3	Milligram	mg
4	Ultraviolet	UV
5	Fourier transform infrared	FT-IR
6	Nuclear magnetic resonance	NMR
7	Dimethyl sulphoxide	DMSO
8	Dimethylformamide dimethyl acetal	DMF-DMA

CHAPTER 1
INTRODUCTION

1.Introduction:

Azaheterocycles constitute wide range of important class of compounds. In particular, pyridine and pyrimidine derivatives constitute a large number of pharmaceuticals, natural products and functional materials (Katritzky, Rees, & Scriven, 1996). Several examples of pharmaceutically important compounds contain pyrimidine moiety are trimethoprim, sulfadiazine, Gleevec and Xeloda (capecitabine).(Nadal & Olavarria, 2004) There are also an important example of isolated pyridine containing natural products Diploclidine and nakinadine. Pyridine-derived pharmaceuticals include atazanavir and imatinib mesylate (Deininger & Druker, 2003) drugs have medical application on treatment of human immunodeficiency virus (HIV) and chronic myelogenous leukemia, respectively. Natural and unnatural polymer also have Pyridine and pyrimidine moiety. Over a century, chemists have proposed several methodologies for pyridine and pyrimidine synthesis and also link to continued importance of the pyridine and pyrimidine core in both biological and chemical fields. Present work is concerned with the synthesis of pyridine and pyrimidine derivatives.

CHAPTER 2

REVIEW OF LITERATURE

2. Literature review:

2.1. General approaches for synthesis of pyridines:

Historically many pyridines were synthesized by condensation between amide and carbonyl compound.

- In the [5+1] condensation with 1,5-dicarbonyls and ammonia (NH_3) which is served as the nitrogen source.(Kelly & Lebedev, 2002)

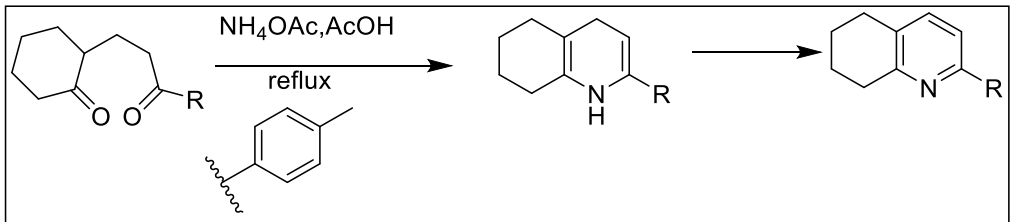


Figure-1. The [5+1] condensation route to substituted pyridine.

- [2+2+1+1] Hantzsch pyridine synthesis:(Hantzsch, 1882)

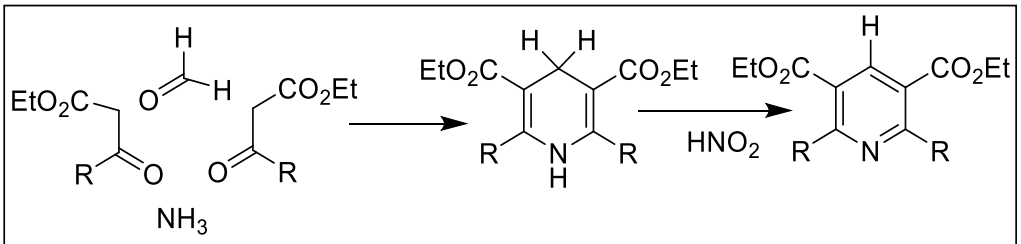


Figure 2. The [2+2+1+1] Hantzsch pyridine synthesis

- [3+3] condensation of 1,3 dicarbonyls with a vinylogous amide:(Baumgarten & Dornow, 1939)

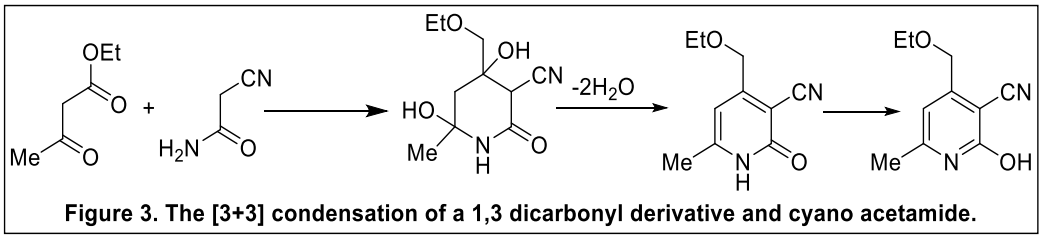


Figure 3. The [3+3] condensation of a 1,3 dicarbonyl derivative and cyano acetamide.

- Boger *et al*. have developed a [4+2] aza-Diels-Alder reaction between enamines and 1,2,4 triazine.(Boger, Panek, & Meier, 1982)

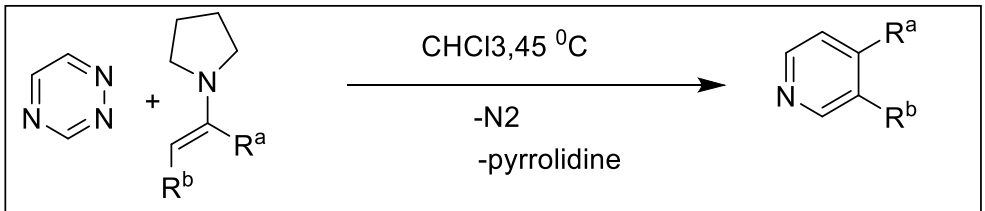


Figure 4. The [4+2] aza-Diels-Alder approach to pyridine derivatives.

- Electrocyclization 6π-electrocyclization process:(Hibino et al., 1992)

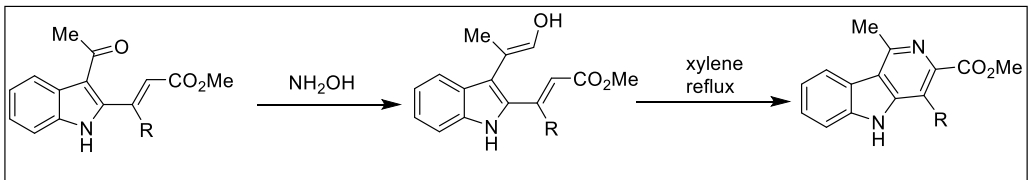


Figure 5. The [4+2] rhodium-mediated synthesis of pyridine.

- Chichibabin reaction:(Chichibabin & Zeide, 1914)

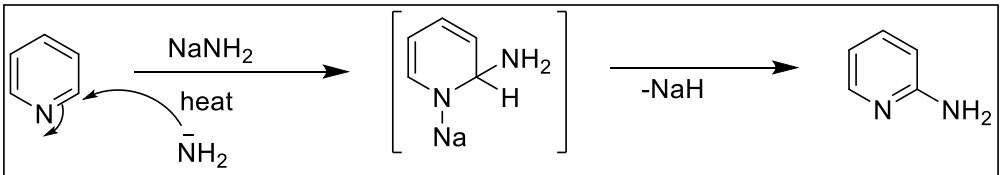


Figure 6. The Chichibabin reaction

2.2. Recent Advances in Pyridines Synthesis:

- Hu *et al*. have reported temperature dependent [5+1] approach to 1,3,5-trisubstituted pyridines.(Hu, Zhang, Yuan, & Liu, 2008)

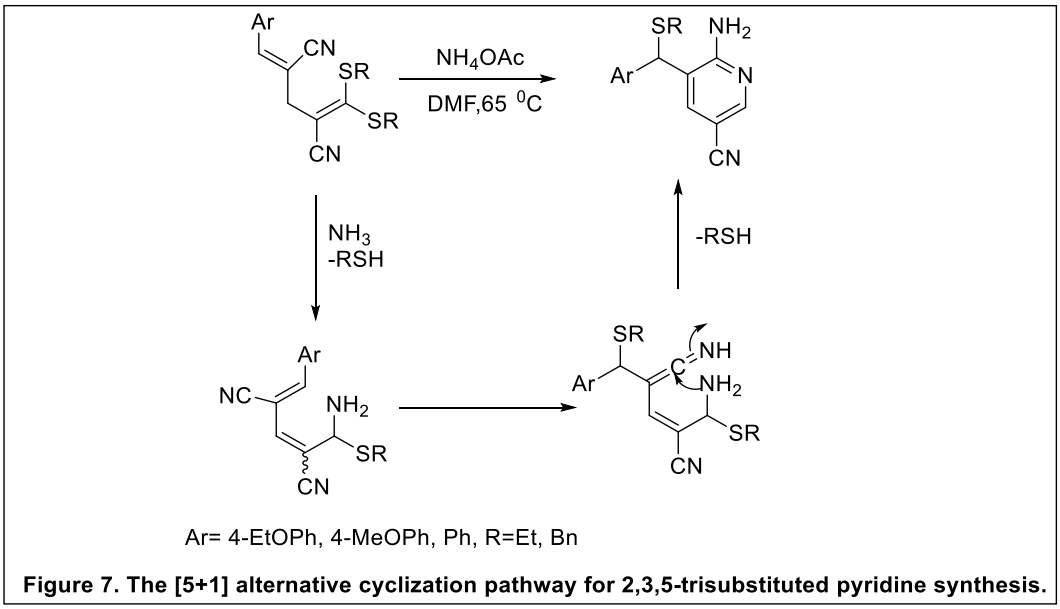


Figure 7. The [5+1] alternative cyclization pathway for 2,3,5-trisubstituted pyridine synthesis.

- Craig and Henry have reported a new [5+1] approach of condensation between 1,5-dicarbonyl with ammonia.(Craig & Henry, 2005)

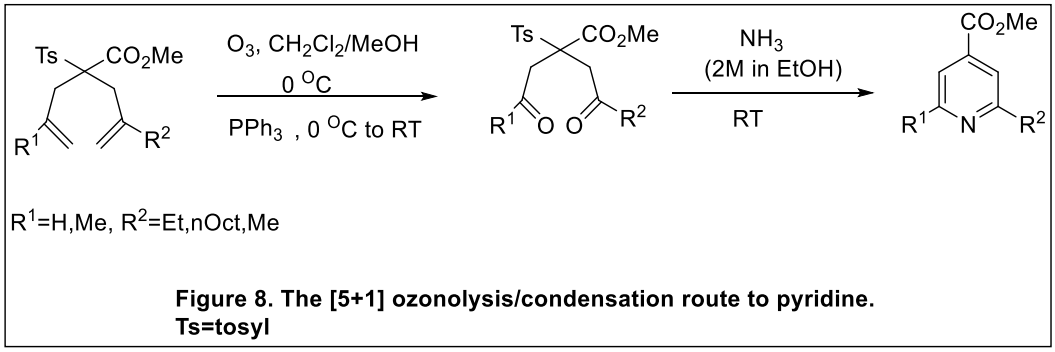


Figure 8. The [5+1] ozonolysis/condensation route to pyridine. Ts=tosyl

- Staforth *et al*. have reported a single step synthesis of alkyl, aryl, heteroatom, and ester 2,3,5-substituted pyridines as a good yield.(Stanforth, Tarbit, & Watson, 2004)

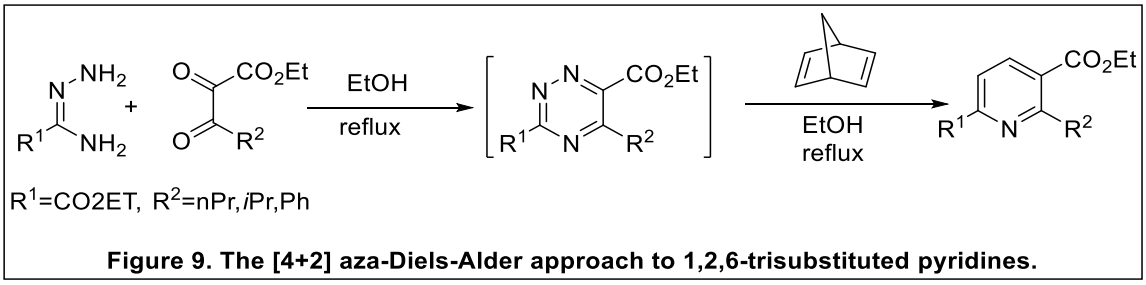


Figure 9. The [4+2] aza-Diels-Alder approach to 1,2,6-trisubstituted pyridines.

- Lu *et al*. have described a [4+2] approach of cycloaddition between 1-aza-1,3-butadiene and α,α-dicyanoalkenes.(Lu et al., 2008)

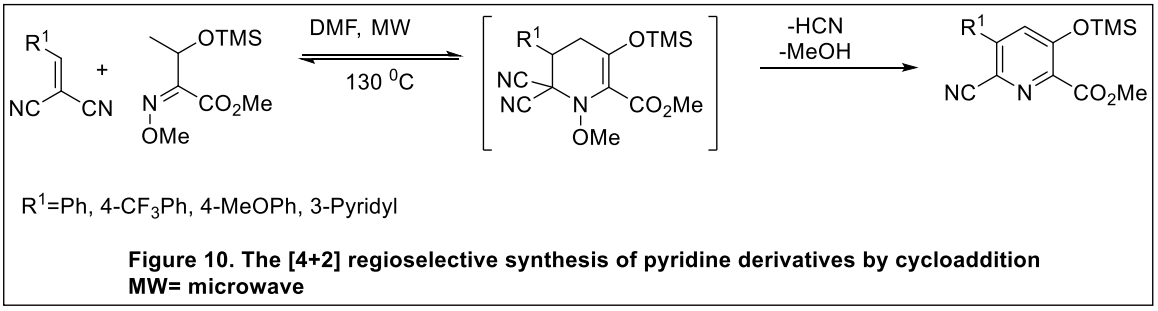


Figure 10. The [4+2] regioselective synthesis of pyridine derivatives by cycloaddition
MW= microwave

- The Larock group have reported a [4+2] approach of 2,4 di- and 2,4,5-trisubstituted pyridines synthesis. These coupling reaction occurs by vinyl imines with terminal alkynes followed by subsequent copper-catalyzed cyclization.(Roesch & Larock, 2002)

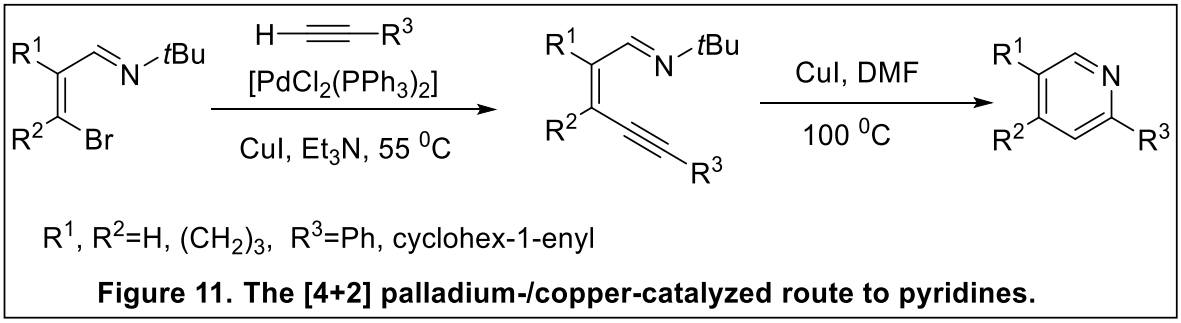


Figure 11. The [4+2] palladium-/copper-catalyzed route to pyridines.

- Ellman *et al*. have reported a single step, transition metal catalyzed [4+2] approach of cycloaddition between α,β-unsaturated imines and alkynes for the synthesis of di-, tri-, tetra-, and pentasubstituted pyridines.(Colby, Bergman, & Ellman, 2008)

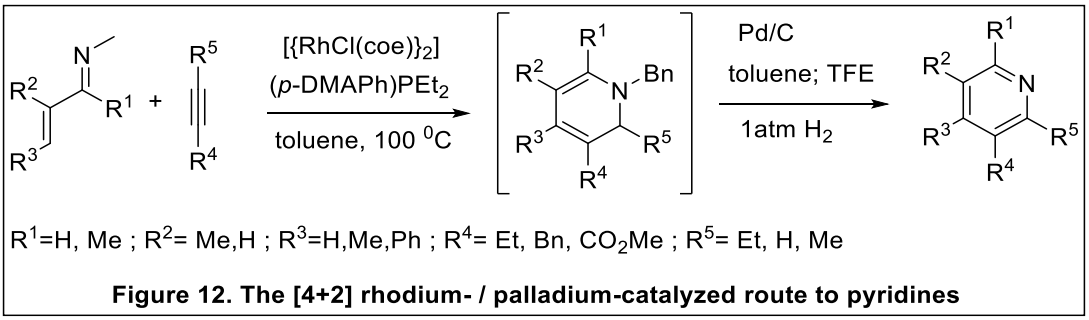


Figure 12. The [4+2] rhodium- / palladium-catalyzed route to pyridines

- Cheng *et al*. have developed a rhodium-catalyzed 6π- Electrocyclization of the aza-triene intermediate and subsequent loss of water for the synthesis of alkyl, aromatic and heteroaromatic substituent of pyridines.(Liu & Liebeskind, 2008; Parthasarathy, Jeganmohan, & Cheng, 2008)

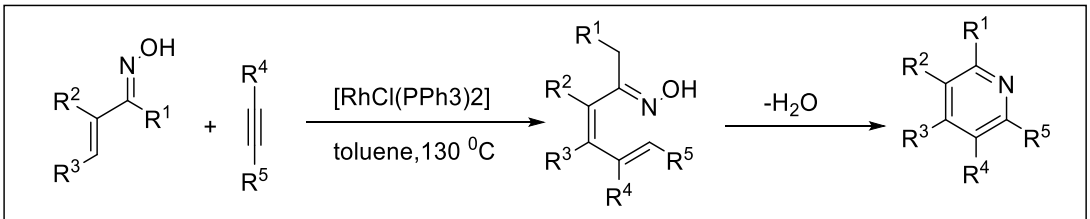


Figure 13. The [4+2] synthesis of pyridine derivatives through a rhodium-catalyzed C-H alkenylation/ electrocyclization reaction sequence.

- Liu and Liebeskind have reported Copper catalyzed [4+2] coupling of α,β-unsaturated ketoxime *O*-pentaflurobenzoates with alkyl- and aryl-substituted alkenyl boronic acid.(Liu & Liebeskind, 2008)

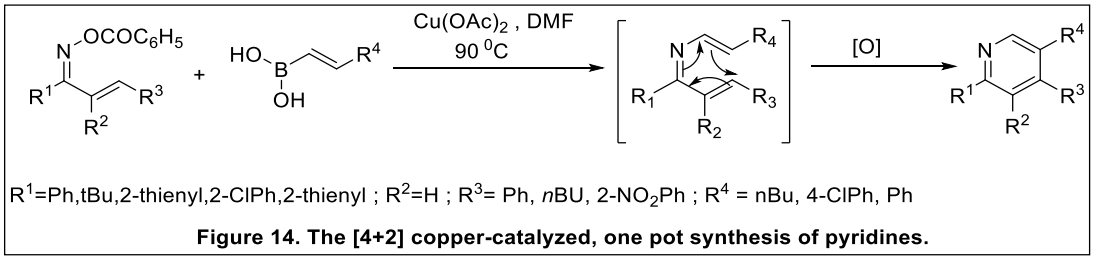


Figure 14. The [4+2] copper-catalyzed, one pot synthesis of pyridines.

- Brandsma *et al*. have synthesized a new [3+3] two step route of pyridines from lithiated allenes or acetylenes and alkyl isithiocyanate.(Nedolya, Schlyakhtina, Zinov'eva, Albanov, & Brandsma, 2002)

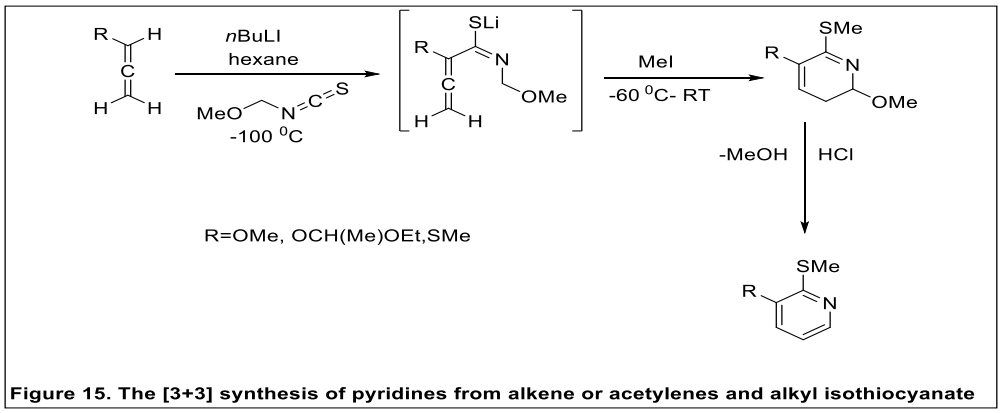


Figure 15. The [3+3] synthesis of pyridines from alkene or acetylenes and alkyl isothiocyanate

- Bagley group reported a single step variation of Bohlmann-Rahtz synthesis utilizing acetic acid(Hill, 2010)

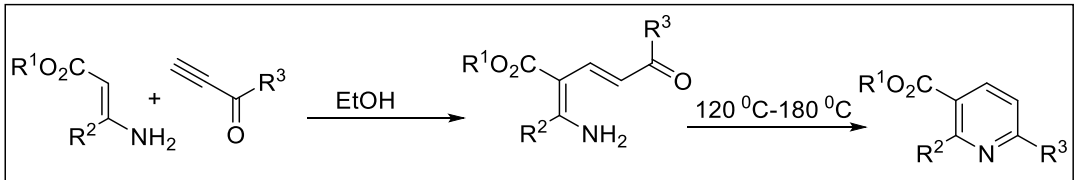


Figure 16. The original [3+3] Bohlmann-Rahtz pyridine synthesis.

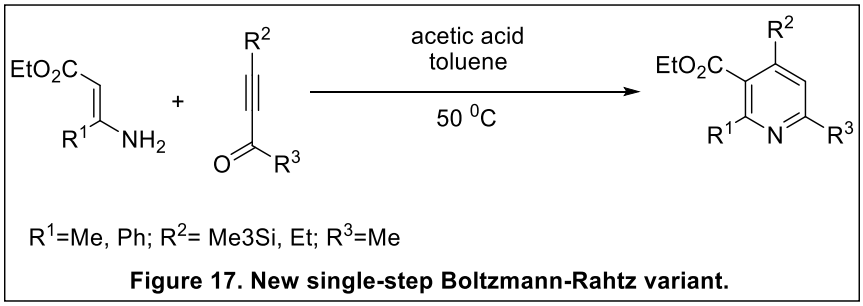


Figure 17. New single-step Boltzmann-Rahtz variant.

- Katritzky *et al*. reported a [3+2+1] approach of tri- or tetra-substituted pyridine synthesis from α-benzotriazolyl ketone and α,β-unsaturated ketone substrates. Fused-pyrimidine also synthesized from this approach.(Katritzky, Abdel-Fattah, Tymoshenko, & Essawy, 1999)

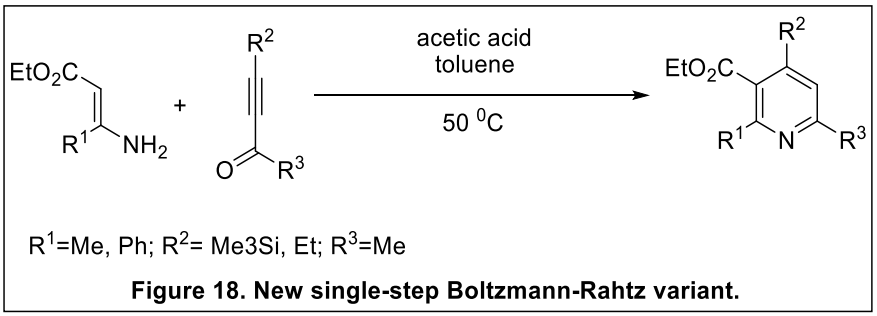


Figure 18. New single-step Boltzmann-Rahtz variant.

- Pyridine was prepared by condensing benzoyl acetone with cyanoacetamide in the presence of sodium ethoxide following the starting compound pyridinecarbonitrile.

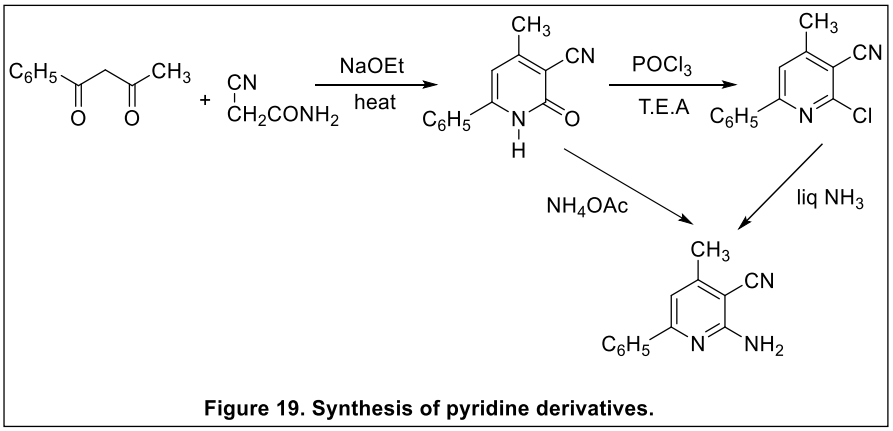


Figure 19. Synthesis of pyridine derivatives.

2.3. General approaches for synthesis of pyrimidines:

- Brugnatelli was synthesized the first pyrimidine derivatives by nitric acid oxidative degradation of uric acid.(Brugnatelli, 1818)

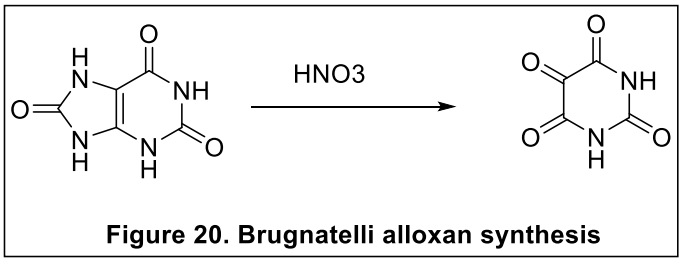


Figure 20. Brugnatelli alloxan synthesis

- In 1848, Frankland and Kolbe reported synthesis of pyrimidine cyanalkine by heating propionitrile with potassium metal.(Frankland & Kolbe, 1848)

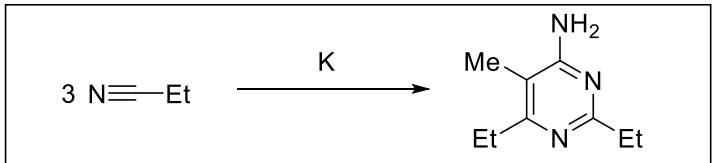


Figure 21. Frankland and Kolbe cyanalkine synthesis

- By refluxing 1,3-dicarbonyl with amidines or guanidines pyrimidine derivatives are synthesized. (Wendelin, Schermanz, Schweiger, & Fuchsgruber, 1983)

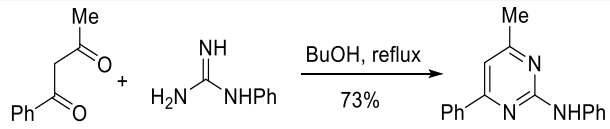


Figure 22.Representative synthesis of a pyrimidine by condensation of a N-C-N fragments and a diketone

- 2-amino 3,4-disubstituted pyrimidine derivative is synthesized by condensation of cyanamide and acetoacetone. (Miller, 1984)

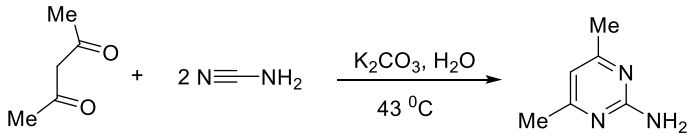


Figure 23. Representative use of cyanamide in condensation with acetoacetone for the synthesis of a pyrimidine.

2.4 Recent advances in pyrimidines synthesis:

- Pinner pyrimidine synthesis: (Pinner, 1887)

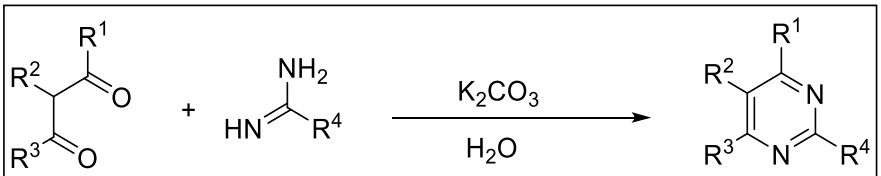


Figure 24. Pinner pyrimidine synthesis

- Ghosh and Katzenellenbogen reported condensation between N,N,N'-tris-(trimethylsilyl)amidine, in place of unsubstituted amidines, with 1,3-dicarbonyl compounds for the synthesis of variety of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidine derivatives.(Ghosh & Katzenellenbogen, 2002)

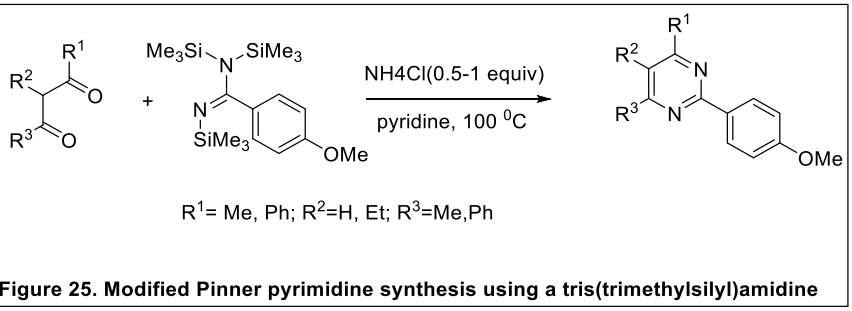


Figure 25. Modified Pinner pyrimidine synthesis using a tris(trimethylsilyl)amidine

- Adamo *et al*. have reported an interesting route to 2,4,6-trisubstituted pyrimidines using amidinium chlorides and diacetylenic ketoesters. Condensation between amidinium chloride and diacetylenic ketoesters afforded the trisubstituted pyrimidine derivatives with alkyl, aromatic, and heteroatom substituents. (Adamo, Adlington, Baldwin, Pritchard, & Rathmell, 2003)

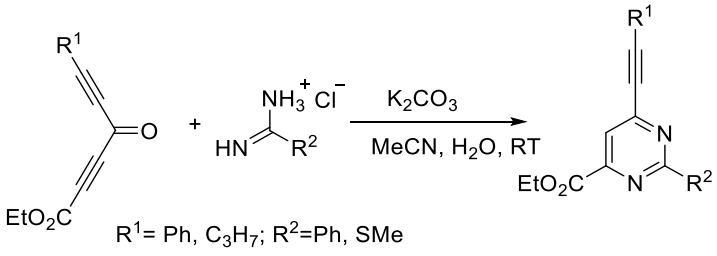


Figure 26. Condensation of diacetylenic ketoesters with amidinium chlorides

- Bellur and Langer reported the synthesis of 4-(3-hydroxyalkyl)pyrimidines by condensation between amidines and 2-alkylidene-tetrahydrofuran derivatives.(Bellur & Langer, 2006)

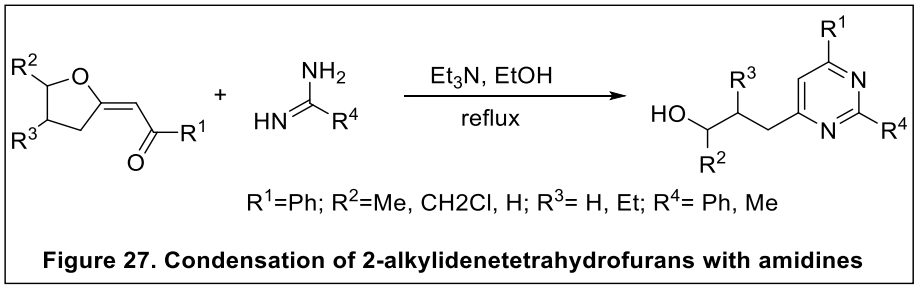


Figure 27. Condensation of 2-alkylidenetetrahydrofurans with amidines

- Zhichkin *et al*. reported a two-step route to 2- substituted pyrimidine-5-carboxylic esters. A number of pyrimidine derivatives were prepared by direct condensation of amidinium chlorides with the sodium salt of 2-dimethoxymethyl-3-hydroxy-acrylic acid methyl ester. (Zhichkin, Fairfax, & Eisenbeis, 2002)

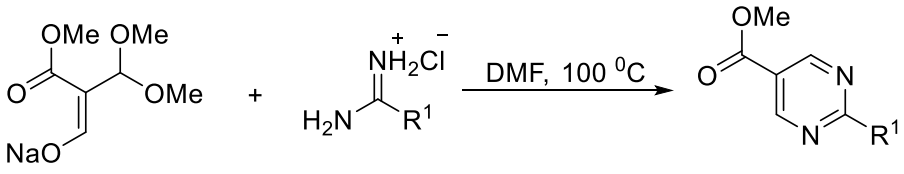


Figure 28. Synthesis of pyrimidine-5-carboxylic acid derivatives

- Molteni *et al*. reported the synthesis of 2,4,5-trisubstituted pyrimidines by condensation between cyclic 1,3-diketones ,amidinium chlorides and dimethylformamide dimethyl acetal. This microwave-promoted reaction continues via in situ enamino ketone formation by its condensation with amidinium chlorides.(Molteni *et al*., 2002)

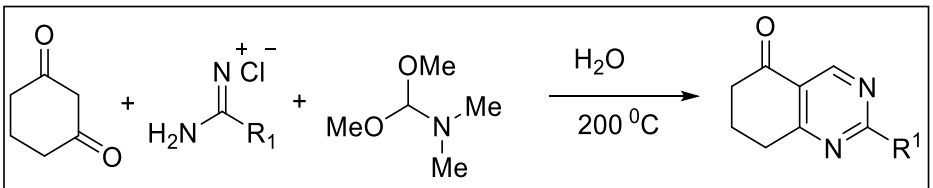


Figure 29. One-pot synthesis of pyrimidine derivatives

- Kiselyov also reported a procedure for the synthesis of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidines by condensation of amidinium or guanidinium chlorides with imine. While aromatic substituents could be introduced at C4 and C6, aliphatic and heteroatom substituents could be introduced at C2 and C5.(Kiselyov, 2005)

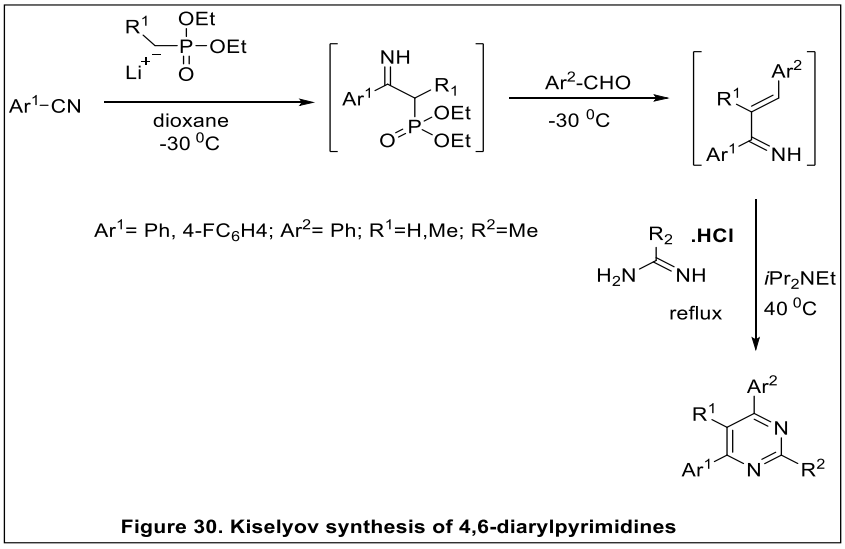


Figure 30. Kiselyov synthesis of 4,6-diarylpyrimidines

- The Muller group have reported a three-component synthesis of 2,4,6-triaryl pyrimidine derivatives. In this coupling reaction electron-deficient iodobenzene undergoes a palladium catalyzed Sonogashira cross-coupling with prop-2-yn-1-ols and reduction to form enone intermediates. Condensation of this intermediate with amidinium chlorides and consequent isomerization follows the corresponding pyrimidines .(Müller, Braun, & Ansorge, 2000)

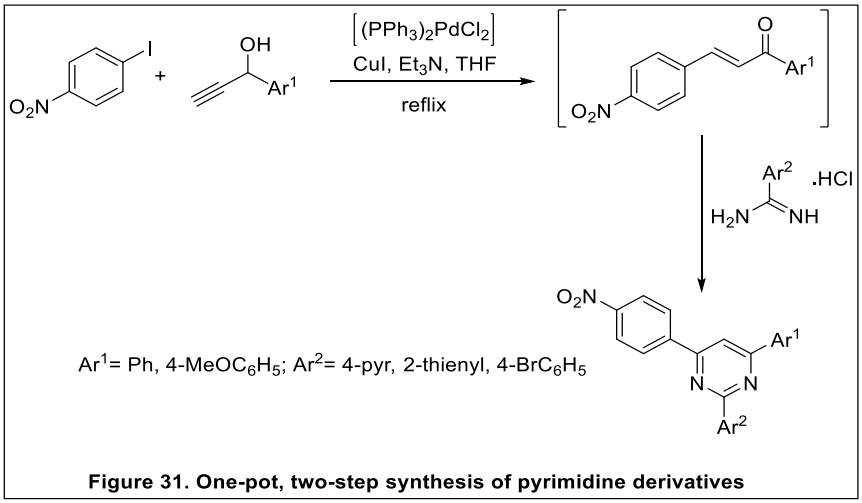


Figure 31. One-pot, two-step synthesis of pyrimidine derivatives

- The Muller group also reported a cross-coupling/addition/cyclocondensation sequence for synthesis of 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines.

The reaction procedure involves a Sonogashira cross-coupling of acid chloride and alkyne to give ynone intermediate. The most reactive Michael acceptor, ynone can undergo base promoted nucleophilic addition by amidinium chloride followed by cyclocondensation to give the di- and tri-substituted pyrimidines with alkyl, aromatic, and heteroatom substitution.(Karpov & Mueller, 2003)

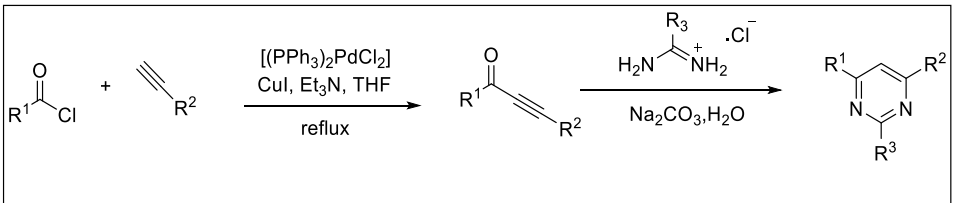


Figure 32. One-pot, two-step synthesis of pyrimidine derivatives

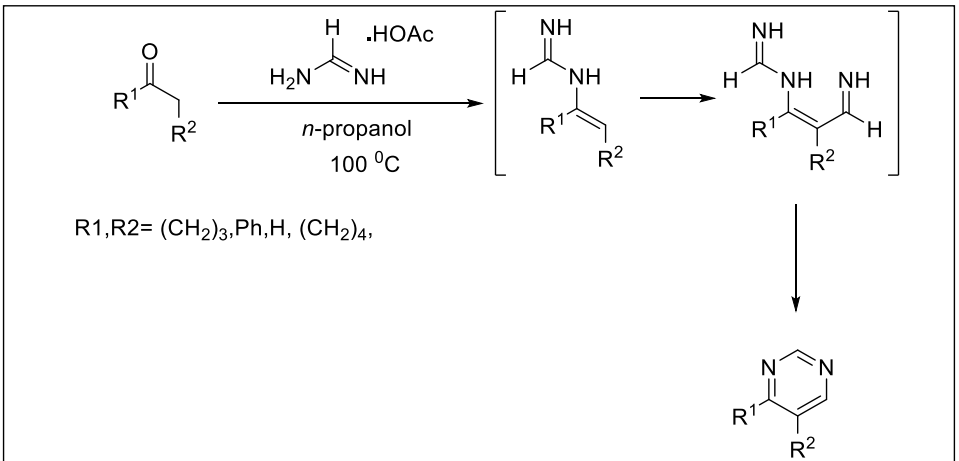


Figure 33. Synthesis of pyrimidine derivatives from ketone and formamidine acetate

- Ingebrigsten *et al*. have reported a methodology for synthesis of mono and di substituted pyrimidines by condensation of two equivalents of formamide with methyl and cyclic ketones. Formation of ammonium formate was unfavorable to the desired reaction, however, the presence of catalytic palladium(II) acetate, triphenylphosphine, and iodobenzene as additives led to its removal from the

reaction mixture. Palladium is supposed to accept a hydride from ammonium formate and reduce iodobenzene.(Ingebrigtsen, Helland, & Lejon, 2005)

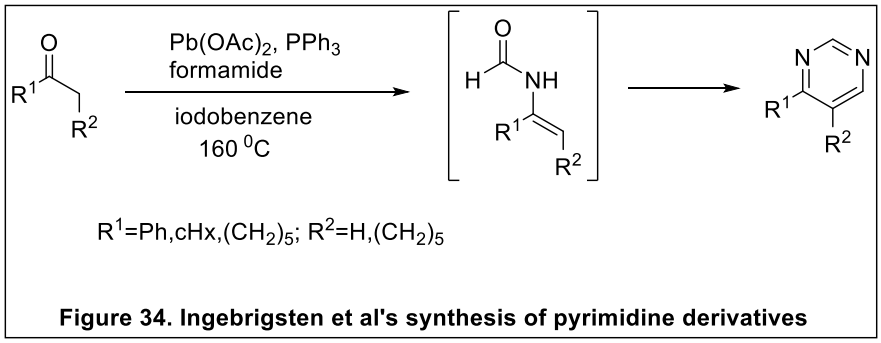


Figure 34. Ingebrigsten et al's synthesis of pyrimidine derivatives

- Tyagarajan and Chakravarty reported microwave-assisted synthesis of various 4-monosubstituted pyrimidines by condensation of two equivalents of formamide with ketone substrates in the presence of p-toluenesulfonic acid and 1,1,1,3,3,3-hexamethyldisilizane. (Tyagarajan & Chakravarty, 2005)

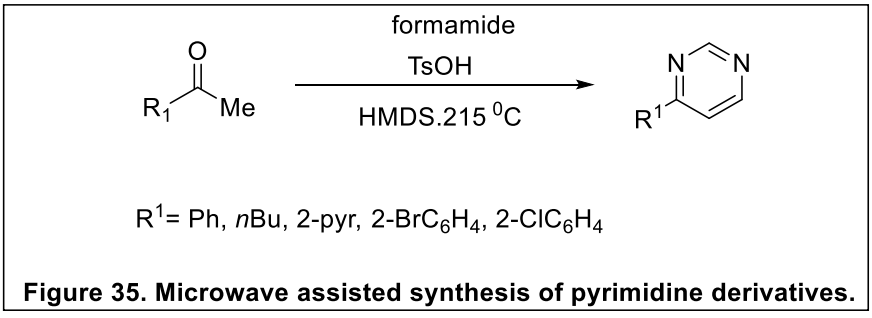


Figure 35. Microwave assisted synthesis of pyrimidine derivatives.

- Martinez *et al*. proposed a pyrimidine synthesis whereby trifluoromethanesulfonic anhydride (Tf_2O) activation of ketone substrates followed by nucleophilic addition of two equivalents of nitriles led to 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted products. Ketone activation was supposed to afford a (trifluoromethanesulfonyloxy)carbenium ion. Nucleophilic addition of two aliphatic or aromatic nitrile equivalents forms nitrilium species that undergo cyclization and loss of triflouromethanesulfonic acid. This process

has been extended to both aliphatic and aromatic acyclic and alicyclic ketones.(Garcia Martinez et al., 1992)

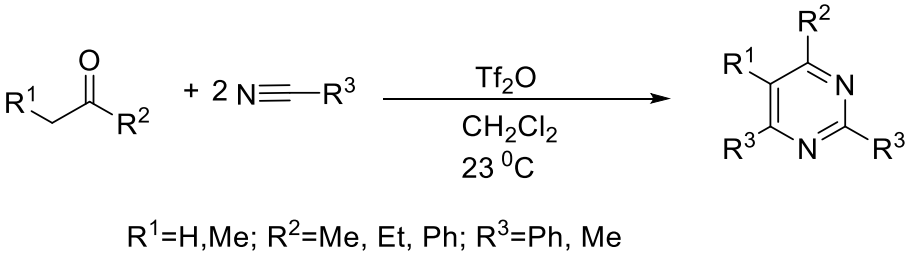


Figure 36. Synthesis of pyrimidine from ketone and nitrile substrate

- Rossi *et al*. reported [3+3] approach to 2,5-disubstituted and 2,4,5-trisubstituted pyrimidines by Aza-Wittig condensation with α,β unsaturated aldehyde followed by diazatriene intermediate. Pericyclization and oxidation (likely autoxidation) afforded the pyrimidine products with whole regiochemical control.(Rossi, Abbiati, & Pini, 1999)

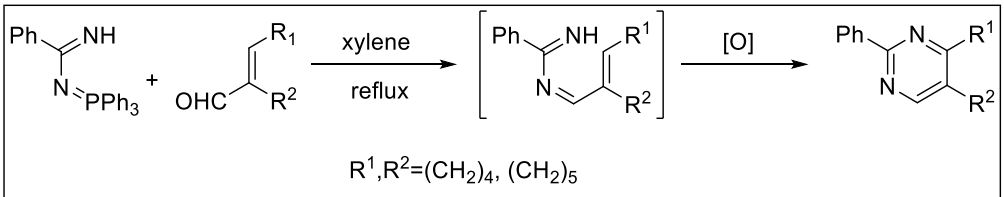


Figure 37. One-pot synthesis of pyrimidine using iminophosphoranes

- Another scientist group have also reported a mild and convergent single-step pyrimidine synthesis based on amide activation with Tf_2O in conjunction with 2-chloropyridine (2-ClPyr).

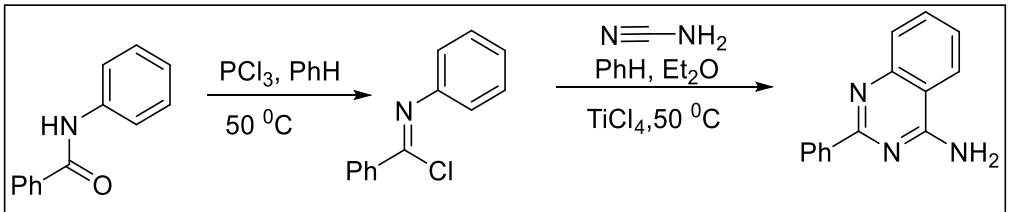
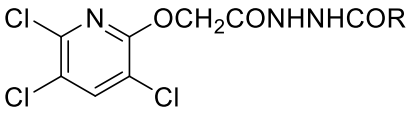


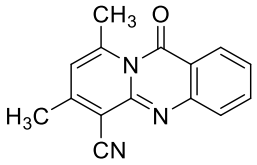
Figure 38. Two step fused pyrimidine synthesis

2.4. Biological application:

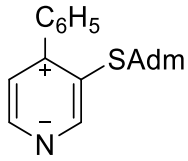
- **Biological application of pyridine derivatives:** Pyridine derivatives have several biological activities which are given below.

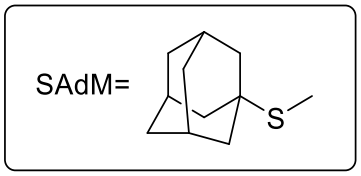
Anti-microbial



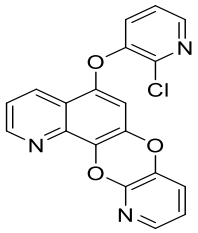


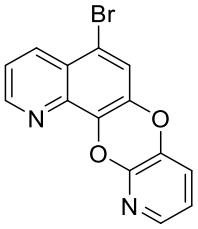
Antioxidant



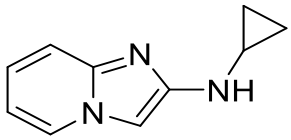


Anti-malarial agent

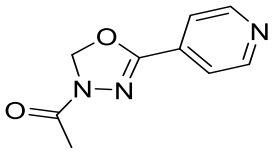


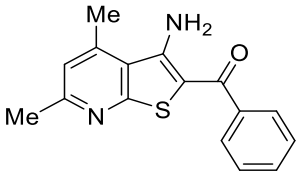


Anti-inflammatory agents

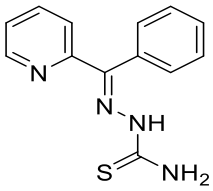


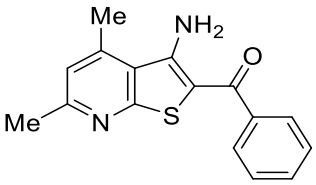
Analgesic potency



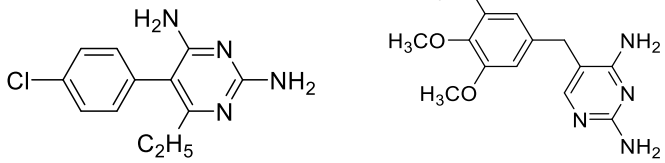
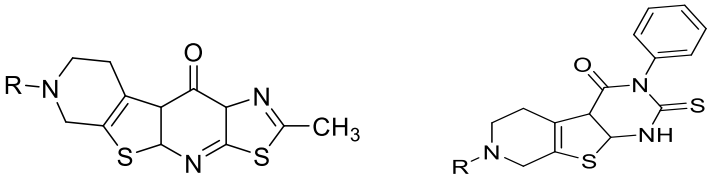
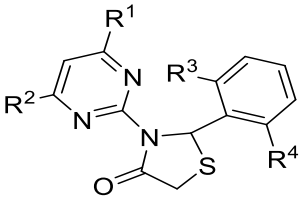
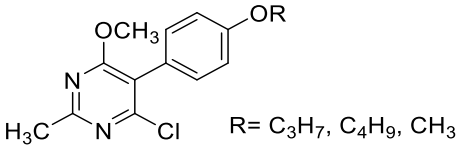
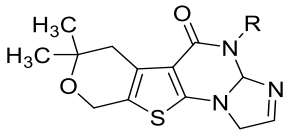


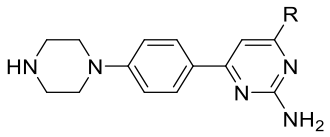
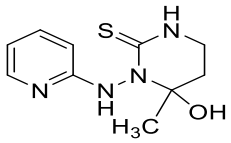
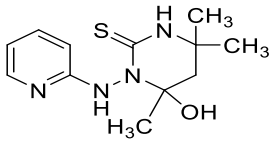
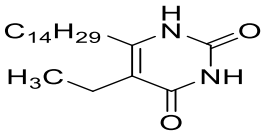
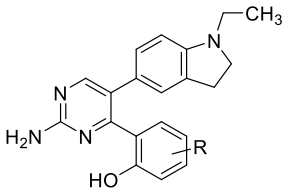
Anticancer agent





2.6. Biological activities of pyrimidine derivatives: Pyrimidine derivatives also have so many medicinal application which is given below.

Antimicrobial activity 
Anti-arrhythmic activity 
Anti-HIV 
Antitumor activity 
Anticonvulsant activity 

Antihistaminic activity

Analgesic agent
 
Anticancer agent
 

CHAPTER 3
RATIONALE AND OBJECTIVES

3.1 RATIONALE:

We have planned to synthesize 2-halonicotinonitrile, 2-aminonicotinonitrile and thieno[2,3-*d*]pyrimidine moieties because these are the basic intermediates for synthesis of several pyridines and pyrimidines, which have various biological application like antimicrobial, anticancer, anti-inflammatory etc.

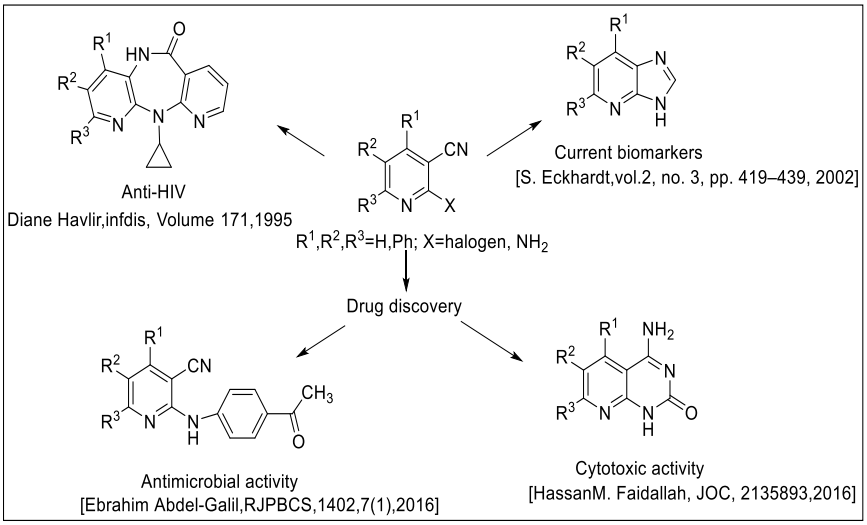
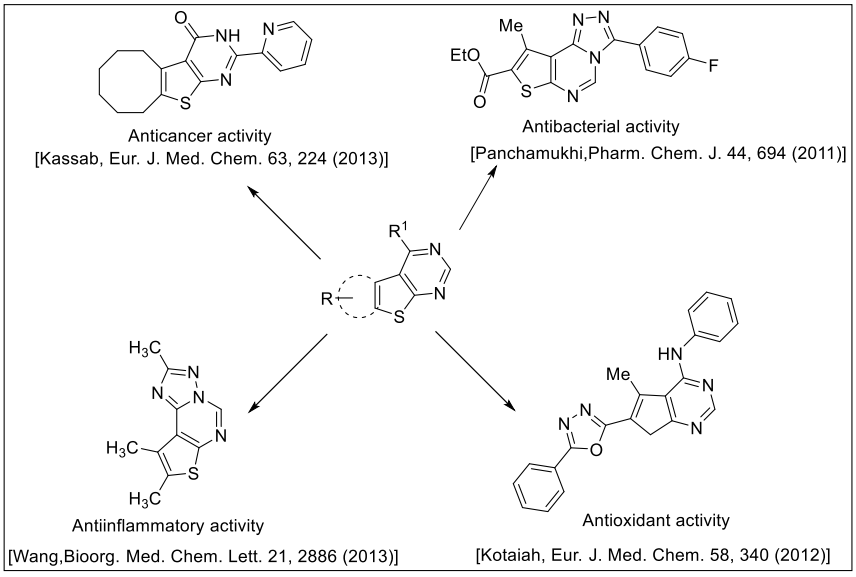


Figure 39. Various biological application of pyridine derivatives

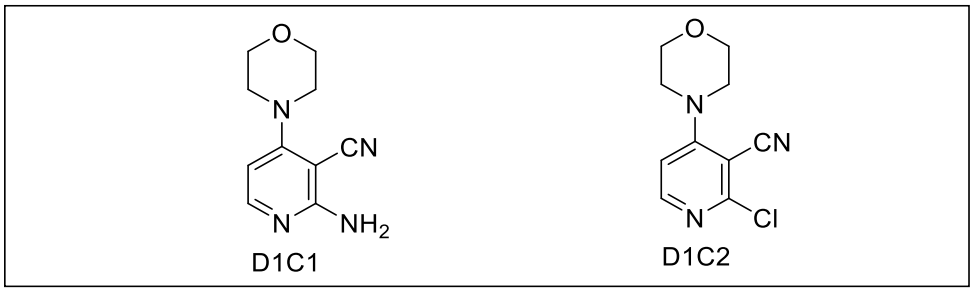


Various biological application of pyridine derivatives

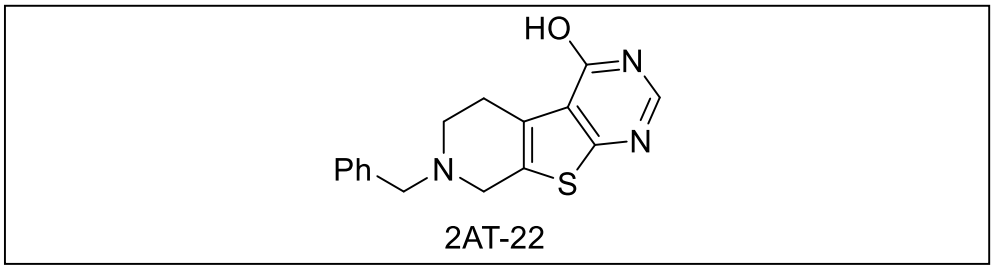
3.2 Objectives:

Objectives of the project is:

A. To synthesize pyridine derivatives (D1C1 and D1C2)



B. To synthesize thieno[2,3-*d*]pyrimidine derivative (2AT-22)



CHAPTER 4
MATERIALS AND METHODS

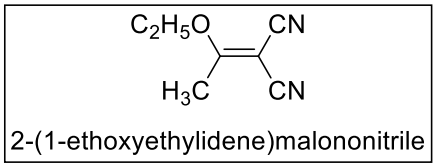
4. Materials and method:

4.1. General:

1. All the reagents were purchased from Sigma- Aldrich, spectrochem Pt. Ltd., Loba-chemie Pt. Ltd., Sisco Research Laboratory and were used without any additional purification.
2. For weighing purpose Analytical balance was used. Rotary evaporator, Heating mantle, Spinot digital hot top and oven were used for the workup of reaction procedures.
3. The progress of reaction was monitored by TLC, petroleum ether/ethyl acetate used as mobile phase on pre-coated TLC plates (Merck) in UV/fluorescent cabinet.
4. Melting points were recorded on Melting point apparatus (SMP-30) with open glass capillary tubes and were uncorrected.
5. Infrared (IR) spectra of compounds were recorded with KBr/neat on a Bruker FT-IR spectrophotometer.
6. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra was recorded at IIT Bhubaneswar in $CDCl_3$/ d_6-DMSO on a Bruker Advance II 400 MHz and 100 MHz respectively using TMS (δ=0) as an internal standard.
7. Mass spectra were recorded on *Shimadzu* GCMS-QP2010 with EI mode available at Central Instrumentation Laboratory (CIL), Central University of Punjab.

4.2 Synthesis:

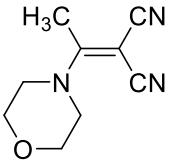
4.2.1. Synthesis of 2-(1-ethoxyethylidene)malononitrile (D1):



2-(1-ethoxyethylidene)malononitrile

To a suspension of malononitrile (18.0343 g, 273 mmol , 1eq) in methanol (50 mL) was added triethyl orthoacetate (50 mL, 273 mmol, 1 eq) .The reaction mixture was heated at 80 ^{o}C for 4 h. The cream colour liquid was formed. After evaporation of methanol this liquid was used for next step without any purification.

4.2.2. Synthesis of 2-(1-morpholinoethylidene)malononitrile (DA1):



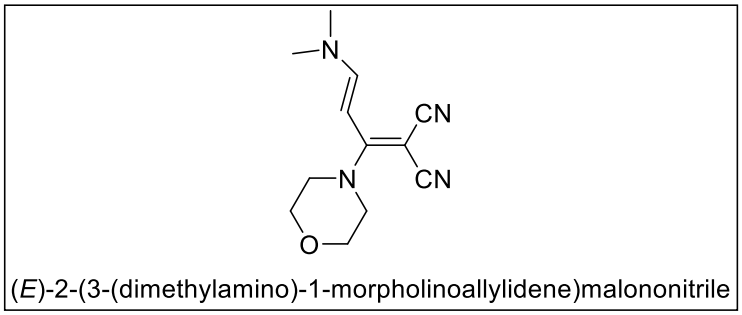
2-(1-morpholinoethylidene)malononitrile

To a suspension of D1 (15 mL, 122 mmol,1 eq) in THF (30 mL) was added morpholine (10.51 mL, 122 mmol, 1eq) .Then the reaction mixture was refluxed at 60 ^{o}C for 4h.The light yellow colour liquid formed which was poured into ice water and light yellow colour solid was precipitated out. After filtration this solid was dried and used for next step without any purification. Yield- 95%, Colour-Light-yellow, m.p-91 ^{o}C

IR (KBr,cm^{-1}): 2200 (CN)

MS (EI): m/z: 177[M^{+}], 78 (base peak)

4.2.3. Synthesis of 2-(3-(dimethylamino)-1morpholinoallyllidene)malononitrile (DB1):



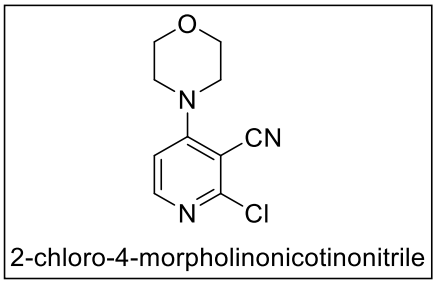
(*E*)-2-(3-(dimethylamino)-1-morpholinoallylidene)malononitrile

To a suspension of DA1 (8 g, 45.15 mmol, 1 eq) was added dimethylformamide dimethyl acetal [DMF.DMA] (9.045 mL, 67.71 mmol, 1.5 eq). The reaction mixture was refluxed at 67 ^{o}C for 4 h. The red colour liquid mixture formed which was poured into ice water and red colour solid was precipitated out. After filtration this solid was dried and used for next step without any purification.Yield-85%, Colour- Red, m.p- 105 ^{o}C

IR (KBr, cm^{-1}): 2185 (CN)

MS (EI): m/z: 232 [M^{+}], 81 (base peak)

4.2.4. Synthesis of 2-chloro-4-morpholinonicotinonitrile (D1C1):



2-chloro-4-morpholinonicotinonitrile

To a suspension of DB1 (2 g) was added conc. HCl (10 mL). The reaction mixture was refluxed at 60 ^{o}C for 3 h. After completion of reaction the liquid mixture was poured into ice water and white colour solid was precipitated out. After filtration the solid had been left for dried up.Yield-80%, Colour-white, m.p- 156 ^{o}C

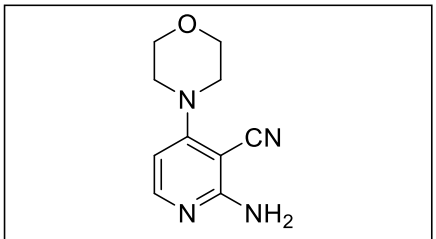
IR (KBr, cm^{-1}): 1732 (CN)

^{1}H NMR (400MHz, $CDCl_3$, TMS=0) δ: 8.18 (1H, d, J=6 Hz), 6.70 (1H, t, J=6 Hz), 3.88 (4H, t, J=4.8 Hz), 3.55 (4H, t, J=4.8 Hz).

^{13}CNMR (100MHz, $CDCl_3$, TMS=0) δ: 160, 155, 151, 115, 110, 98, 66, 49.

MS (EI): m/z: 223 [M^+], 138 (base peak)

4.2.5. Synthesis of 2-amino-4-morpholinonicotinonitrile (D1C2):



2-amino-4-morpholinonicotinonitrile

To a suspension of DB1 (2 g) was added liquid ammonia (10 mL). The reaction mixture was refluxed at 60 ^{o}C for 3 h. After completion of reaction the liquid mixture was poured into ice water and grey colour solid was precipitated out. After filtration the solid had been left for dried up.Yield-80%, Colour- Grey, m.p- 120 ^{o}C

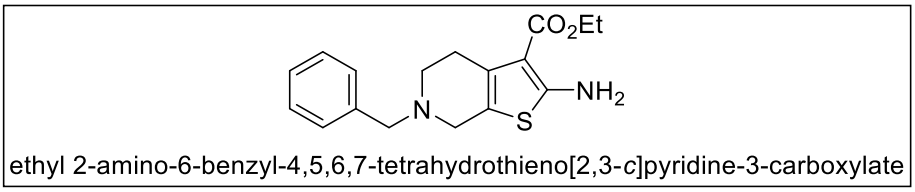
IR (KBr,cm^{-1}): 3353(NH_2), 1622 (NH_2 bend), 2199 (CN)

^{1}H NMR (400 MHz, $CDCl_3$, TMS=0) δ: 7.93 (1H, d, J= 6 Hz), 6.12 (1H, d, J =6 Hz), 3.85 (4H, t, J= 4.4 Hz), 3.45 (4H, t, 4.8 Hz), 5.28 (s, NH_2)

^{13}C NMR (100MHz, $CDCl_3$, TMS=0) δ: 161, 160, 152, 117, 102, 86, 66, 51.

MS (EI): m/z: 204 [M^+], 119 (base peak)

4.2.6. Synthesis of ethyl-2-amino-6-benzyl-4,5,6,7-tetrahydrothieno-[2,3-*c*]-pyridine-3-carboxylate (2-AT2):



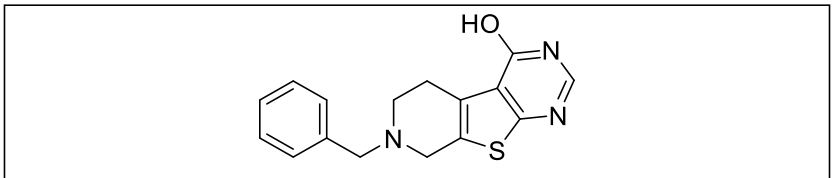
ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

To a suspension of N-Benzyl-4-piperidone (10 mL, 56.01 mmol,1 eq) in ethanol (50 mL) was added ethyl cyanoacetate (6.5 mL,61.61 mmol,1.1eq) , sulfur (1.79 g, 56.01 mmol, 1eq) and base diethylamine (6.371 mL ,61.61 mmol , 1.1eq) drop wise. The reaction mixture was stirred at 60 ^{o}C for 4h. The reaction mixture was converted to dark brown colour which was poured to the ice water and yellow colour solid was precipitated out. After filtration yellow solid was dried and used for next step without any purification. Yield: 70%, Colour-Yellow, m.p- 148 ^{o}C

IR (KBr, cm^{-1}): 3326 (NH_2), 1663(NH_2 bend), 1735 (C=O stretch in ester)

MS (EI): m/z: 315 [M^{+}], 91 (base peak)

4.2.7.Synthesis of 7-benzyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-ol (2-AT22):



7-benzyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-ol

To a suspension of 2-AT2 (8 g) was added formamide (12 mL). The reaction mixture was refluxed at 180 ^{o}C for 12 h. After completion of reaction mixture was poured to the ice water and grey colour solid (2-AT22) was precipitated out.Yield-90%, Colour-Grey, m.p- 160 ^{o}C

IR (KBr, cm^{-1}): 3396 (OH stretch), 1763 (C=N)

^{1}H NMR (400 MHz, d_6-DMSO, TMS=0) δ: 12.379 (1H,s), 8.033 (1H,s), 7.30 (5H,m, J=4 Hz), 3.693 (2H, s), 3.603(2H, s), 2.93(2H, d, J= 4Hz), 2.75(2H, d, J=6 Hz)

^{13}C NMR (100MHz, d_6-DMSO, TMS=0) δ: 163.35, 158.09, 145.60, 138.57, 130.29, 129.71, 129.24, 128.75, 127.55, 122.79, 61.29, 51.42, 49.41, 26.10

MS (EI): m/z: 297[M^+], 91(base peak)

CHAPTER 5
RESULTS AND DISCUSSION

5 Result and Discussion

5.1 Synthesis

5.1.1 For the synthesis of targeted compounds D1C1 and D1C2, we proposed the mechanism route given below:

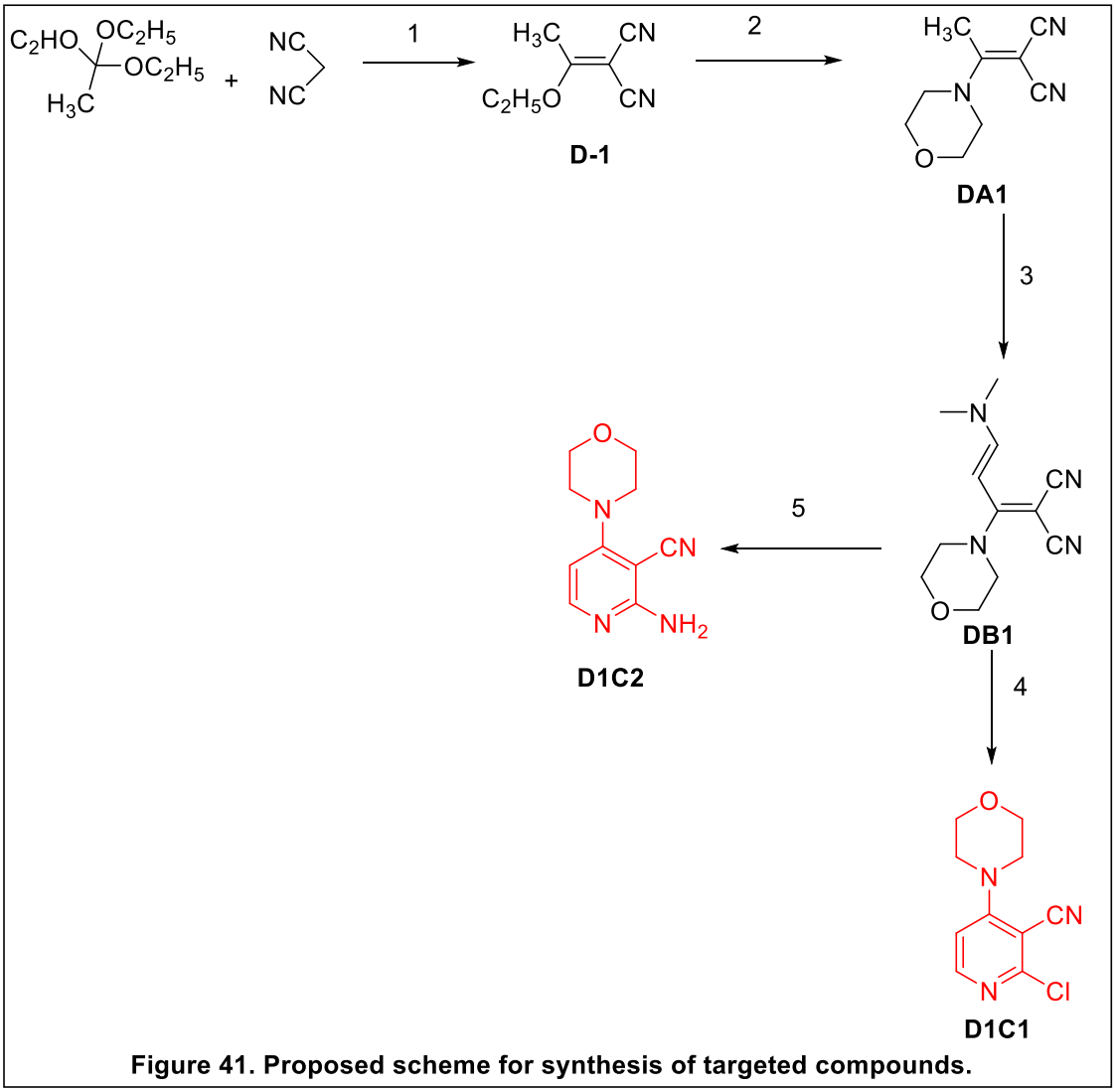


Figure 41. Proposed scheme for synthesis of targeted compounds.

5.1.2 Synthesis of 2-(1-ethoxyethylidine)malononitrile [D-1]:

In the step 1 the mixture of the triethyl orthoacetate and malononitrile was refluxed in MeOH as a solvent to get 2-(1-ethoxyethylidine)malononitrile and the progress of the reaction was monitored by TLC.

Mechanistically, the above reaction involves the nucleophilic attack of one negative charge of the carbon of malononitrile to the electrophilic carbon of triethyl orthoacetate leading to the formation of D-1 via various intermediate as shown in figure 42 with loss of two molecules of EtOH.

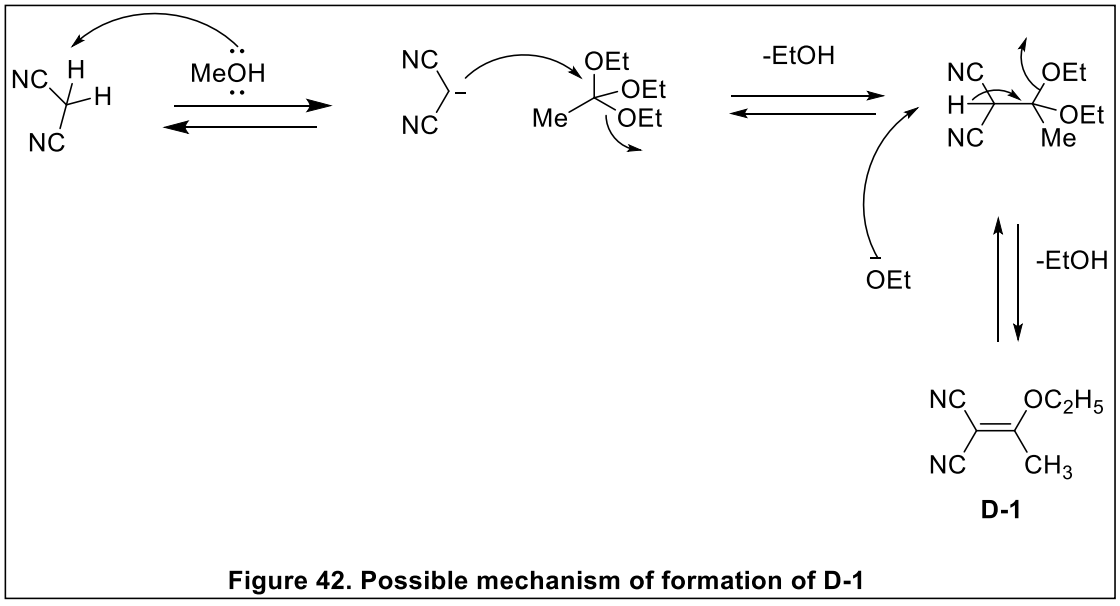


Figure 42. Possible mechanism of formation of D-1

5.1.3 Synthesis of 2-(1-morpholinoethylidene)malononitrile [DA1]:

Compound D-1 was treated with morpholine in THF as a solvent which led to the formation of 2-(1-morpholinoethylidene)malononitrile. The compound was used for next step without any purification.

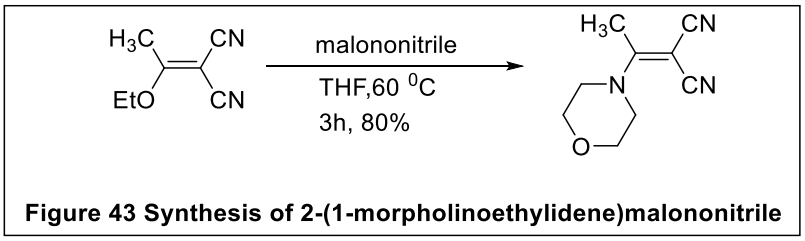


Figure 43 Synthesis of 2-(1-morpholinoethylidene)malononitrile

The formation of DA1 can be mechanistically predicted as the nucleophilic attack of one of the nitrogen's lone pair of morpholine on electrophilic carbon of 2-(ethoxyethylidine)malononitrile via intermediate as shown in Figure 44 with loss of one molecule of EtOH.

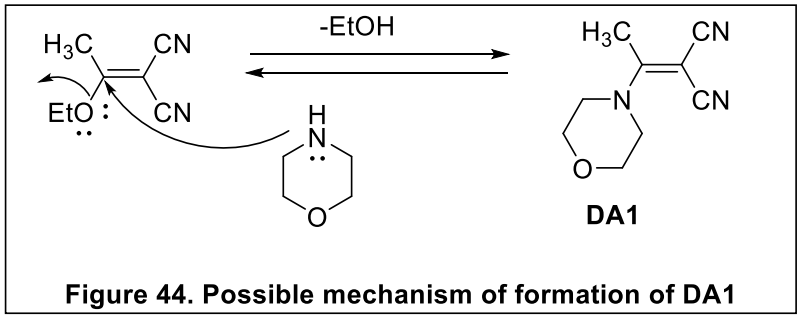


Figure 44. Possible mechanism of formation of DA1

Formation of DA1 was confirmed by IR and mass spectroscopy.

IR spectrum showed the characteristic peak of cyanide at 2200 cm^{-1}.

Mass spectrum of the compound showed the peak at 177 [M^+], 78 (base peak).

5.1.4. Synthesis of 2-(3-(dimethylamino)-1-morpholinoallylidene)malononitrile [DB1]:

Compound DA1 was treated with DMF.DMA in THF as a solvent which lead to the formation of (E)-2-(3-(dimethylamino)-1-morpholinoallylidene)malononitrile. The compound was used for next step without any purification.

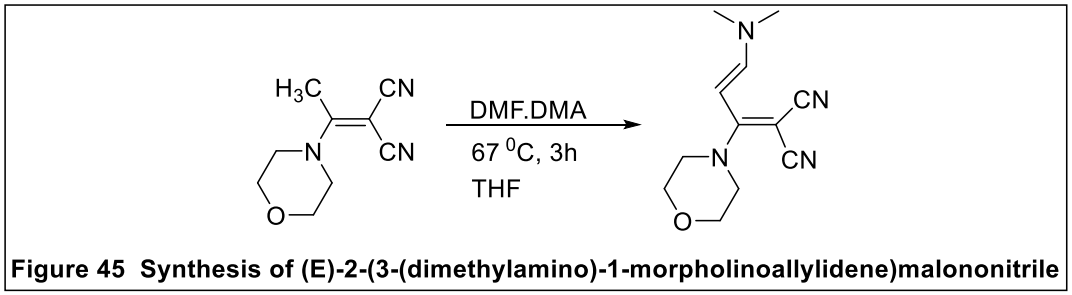


Figure 45 Synthesis of (E)-2-(3-(dimethylamino)-1-morpholinoallylidene)malononitrile

The formation of compound DB1 was mechanistically predicted as shown below.

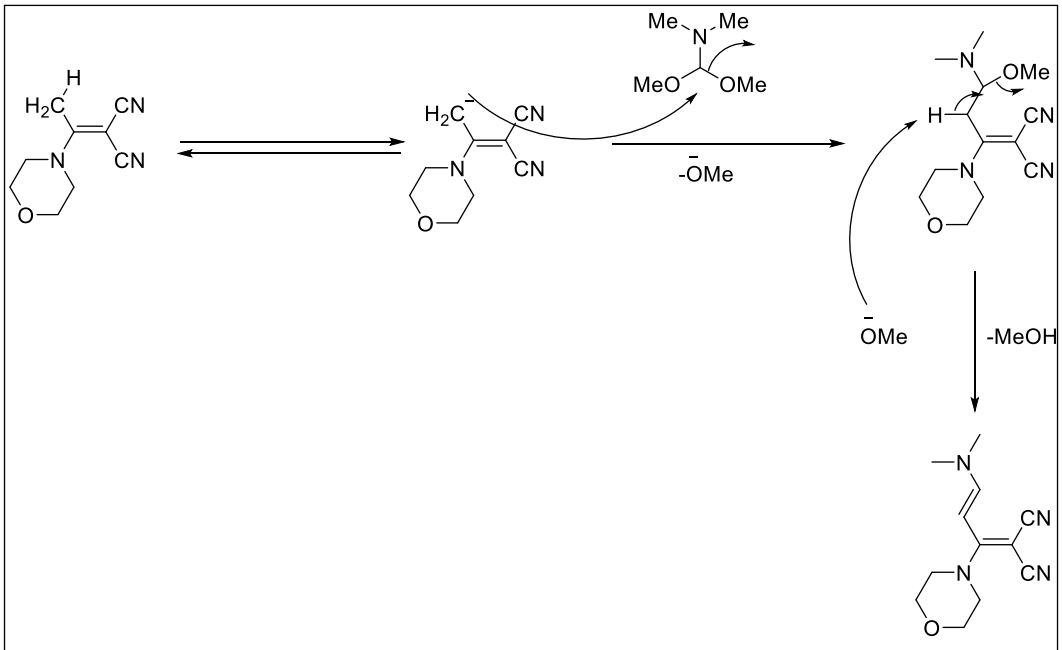


Figure 46. Possible mechanism of formation of DB1

Formation of DB1 was confirmed by IR and mass spectroscopy.

IR spectrum showed the characteristic peak of cyanide at 2185 cm^{-1}.

Mass spectrum of the compound showed the peak at 232 [M^+], 81 (base peak).

5.1.5. Synthesis of 2-chloro-4-morpholinonicotinonitrile [D1C1]:

Compound DB1 was treated with conc.HCl which lead to the formation of 2-chloro-4-morpholinonicotininitrile.

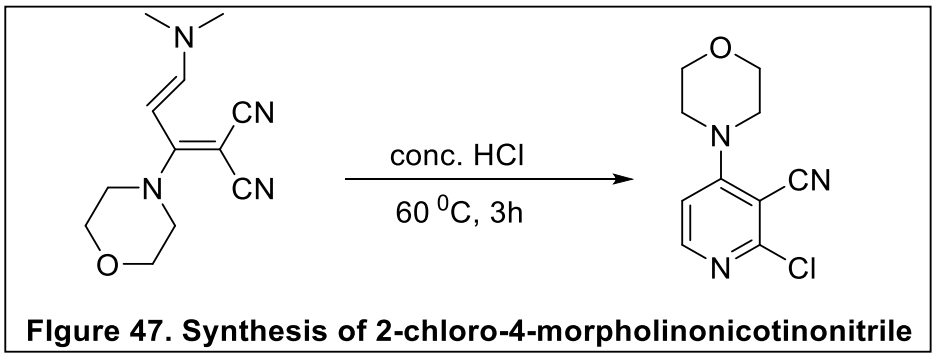


FIgure 47. Synthesis of 2-chloro-4-morpholinonicotinonitrile

The formation of D1C1 was mechanistically predicted as given below.

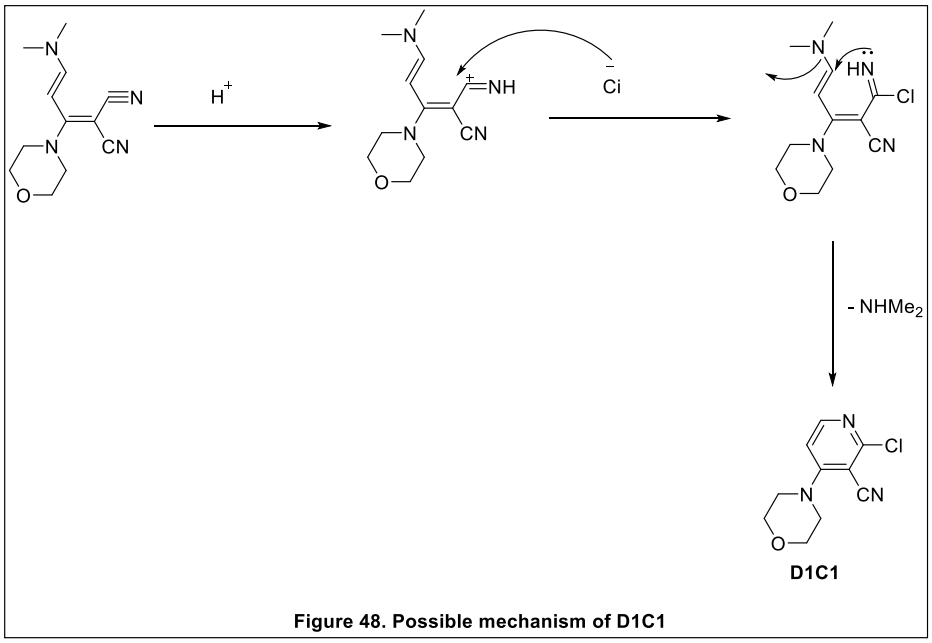


Figure 48. Possible mechanism of D1C1

Formation of D1C1 was confirmed by IR and mass spectroscopy.

IR spectrum showed the characteristic peak of cyanide at 1732 cm^{-1}.

In ^{1}H NMR showed the triplet peak at 3.86 and 3.55 approving the presence of morpholine ring. Due to more electronegative nature of oxygen as compare to nitrogen adjacent hydrogen of oxygen appears to be more deshielded value. 1H NMR showed other peaks at 6.78 and 8.20 due to pyridine ring. Hydrogen which was placed ortho

position in respect to nitrogen give greater chemical shift value than meta position due to more electronegative nature of nitrogen.

^{13}C NMR showed the characteristic peaks of cyanide at 115.44. It also gives other peaks at 66.35, 49.80, 49.76, 160.96, 155.44, 151.57, 110.28, 98.41. Due to more electronegativity of nitrogen, adjacent carbon of nitrogen give more deshielded value. Meta position carbon in respect to nitrogen has less chemical shift value than ortho position in pyridine ring.

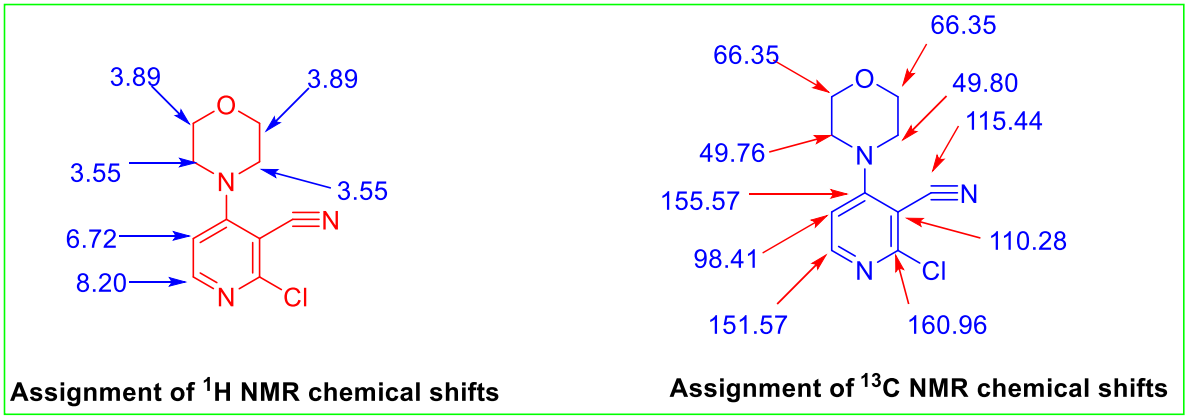


Figure 49.NMR data of compound D1C1

Mass spectrum of the compound showed the peak at 204 [M^+], 119 (base peak).

5.1.6 Synthesis of 2-amino-4-morpholinonicotinonitrile [D1C2]:

Compound DB1 was treated with liq. NH_3 which lead to the formation of 2-amino-4-morpholinonicotininitrile.

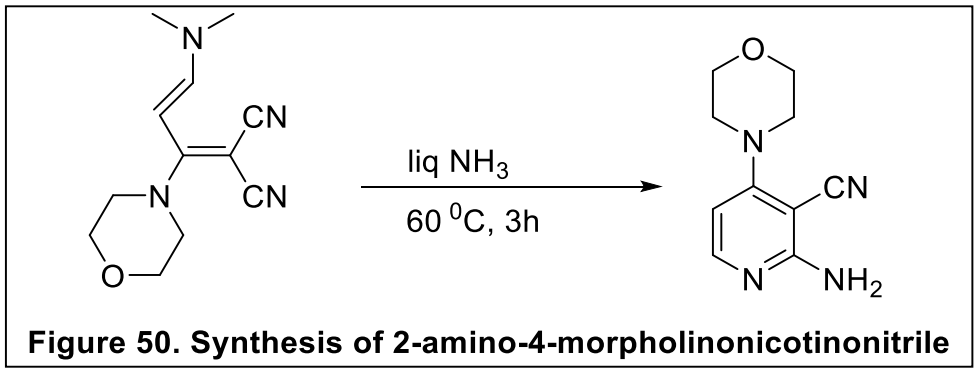


Figure 50. Synthesis of 2-amino-4-morpholinonicotinonitrile

The formation of D1C2 was mechanistically predicted as given below.

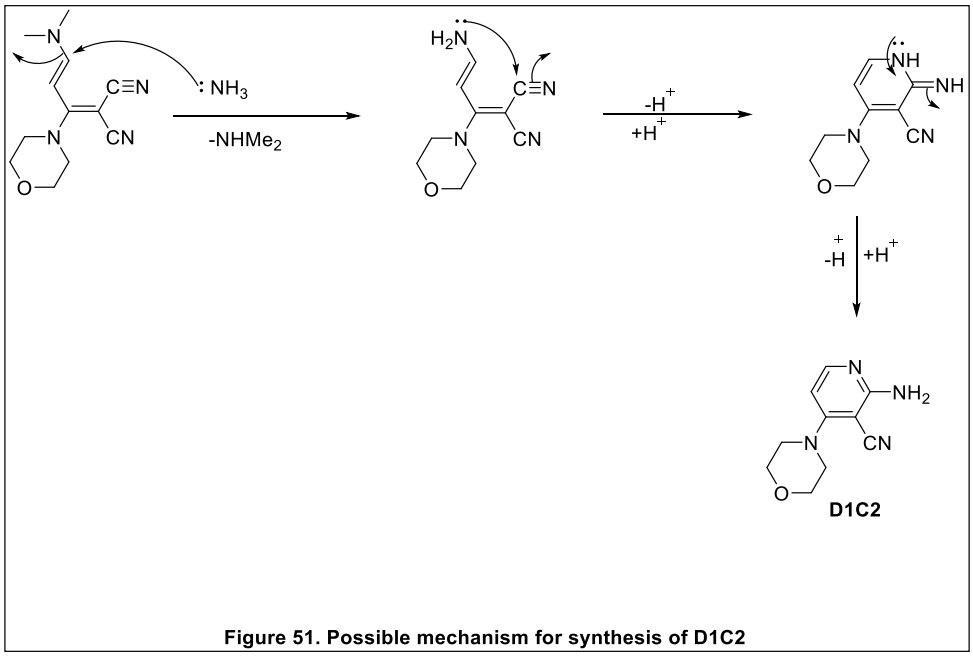


Figure 51. Possible mechanism for synthesis of D1C2

Formation of D1C2 was confirmed by IR, mass and NMR spectroscopy.

IR spectrum showed the characteristics peak of primary amine stretching, bending and cyanide at 3353 cm^{-1}, 1622 cm^{-1}, 2199 cm^{-1}.

In ^{1}H NMR showed the triplet peak at 3.84 and 3.44 approving the presence of morpholine ring. Due to more electronegative nature of oxygen as compare to nitrogen adjacent hydrogen of oxygen appears to be more deshielded value. 1H NMR showed the characteristic peak of ammonia at 5.278 and other peaks at 6.78 and 8.20 due to pyridine ring. Hydrogen which was placed ortho position in respect to nitrogen give greater chemical shift value than meta position due to more electronegative nature of nitrogen.

^{13}C NMR showed the characteristic peaks of cyanide at 117.49. It also gives other peaks at 161.89,160,86, 152.39, 102.13, 86.55, 66.52, 51.18, 49.70, 42.53. Due to more electronegativity of nitrogen, adjacent carbon of nitrogen give more deshielded value. Meta position carbon in respect to nitrogen has less chemical shift value than ortho position in pyridine ring.

Mass spectrum of the compound showed the peak at 223 [M^{+}], 138 (base peak).

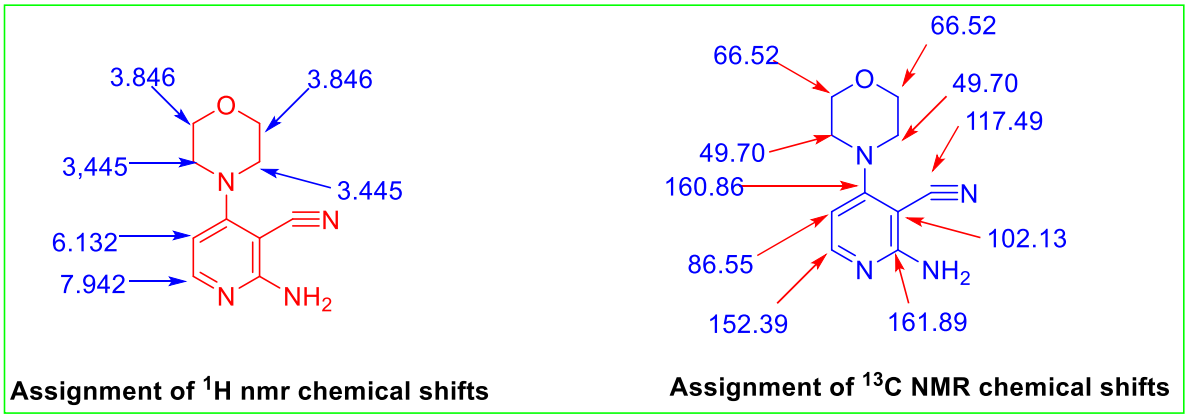


Figure 52, NMR data of D1C2

5.2 For the synthesis of target compound 2-AT22 we proposed the mechanism given below:

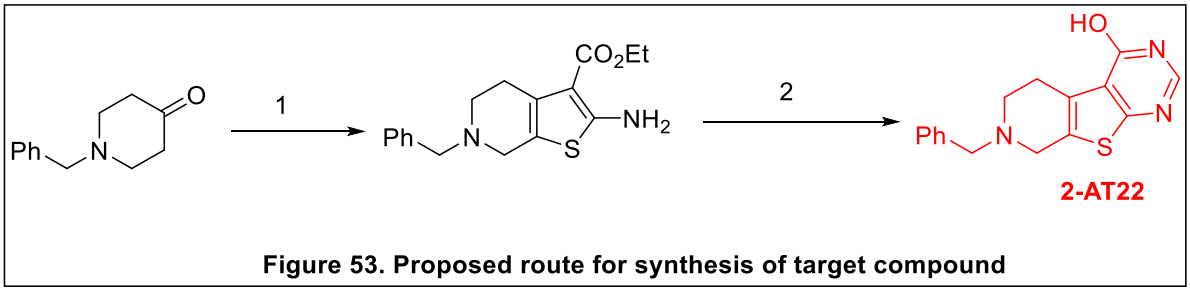


Figure 53. Proposed route for synthesis of target compound

5.2.1 Synthesis of 2-amino-6-benzyl-4,5,6,7-tetrathieno[2,3-*c*]pyridine-3-carboxylate (2-AT2):

In the step 1 the mixture of n-benzylpiperidone and ethyl cyanoacetate was heated at 60 ^{0}C in methanol as solvent and diethylamine acts as a base to get compound 2-AT2 and the progress of the reaction was monitored by TLC.

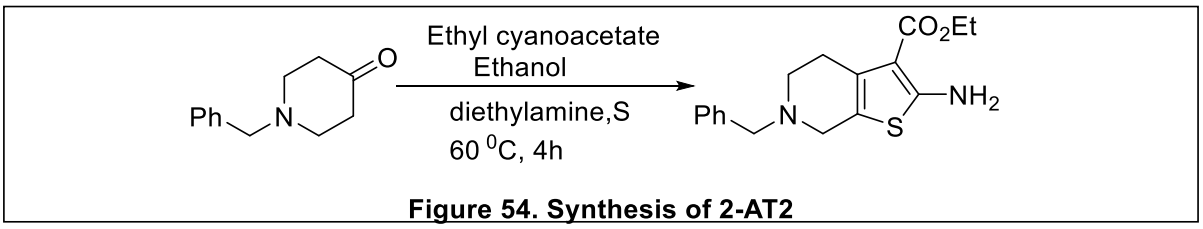


Figure 54. Synthesis of 2-AT2

The 2-AT2 compound was formed by Gewald reaction. At the first step of the gewald reaction ia a knoevenagel condensation of an active methylene group of ethyl cyanoacetate with N-Benzyl-4-piperidone to produce an intermediate. Which is then thiolated at the the γ-methylene group with elemented sulfur. Then the sulfurated compound undergoes ring closure via nucleophilic merceptide attack at the carbon to provide an intermediate. Finally prototopic rearrangement afford 2-aminothiophen as shown below (Figure 55).

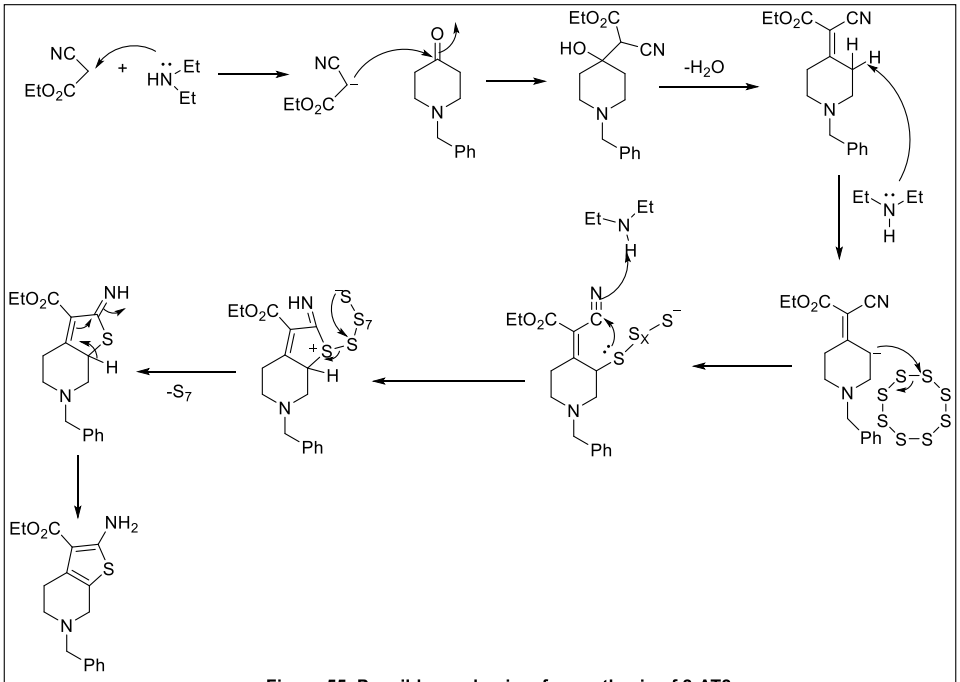


Figure 55. Possible mechanism for synthesis of 2-AT2

Formation of 2-AT2 is confirmed by IR and mass spectroscopy.

IR spectrum showed the characteristic peaks of primary amine stretching, bending and C=O in ester at 3326 cm^{-1},1663 cm^{-1}, 1735 cm^{-1}

Mass spectrum of the compound showed the peak at 315 [M^+], 91 (base peak).

5.2.2 Synthesis of 7-benzyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-ol [2-AT22]:

In step 2 the mixture of 2-AT2 and formamide was heated at 180 ^{0}C for 12h to get the targeted compound 2-AT22.

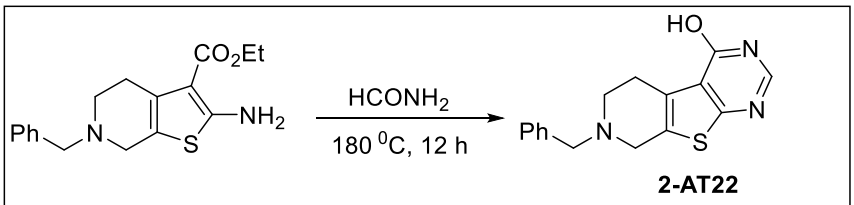


Figure 56. Synthesis of targeted compound 2-AT22

The formation of 2-AT22 can be mechanistically predicted as the nucleophilic attack of one of the lone pair of nitrogen's of formamide to electrophilic carbon of compound 2-AT2, intermediate was formed which is then cyclized with loss of one molecule of H_2O and 2AT22 was formed. (Figure 57).

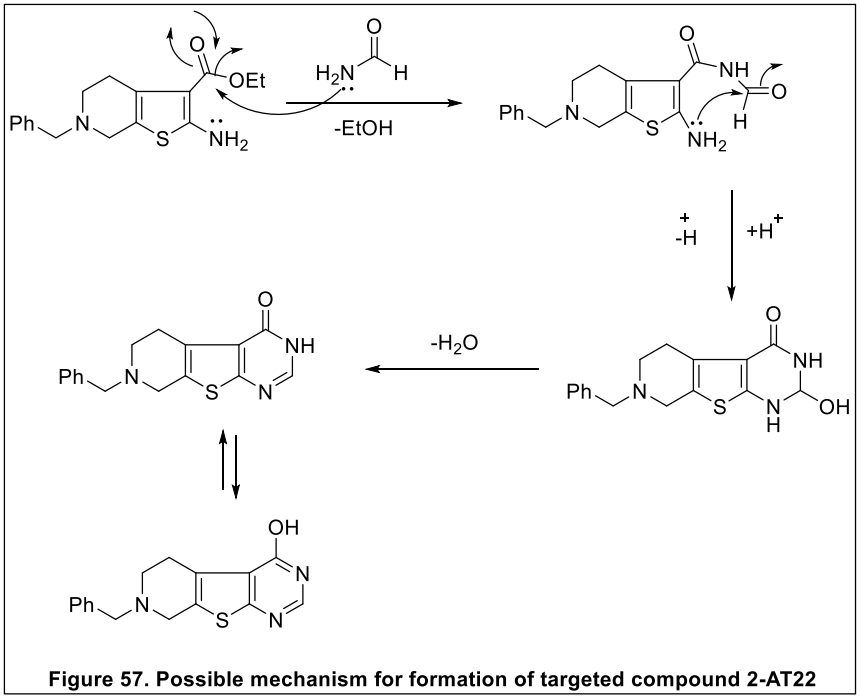


Figure 57. Possible mechanism for formation of targeted compound 2-AT22

Formation of 2-AT22 was confirmed by IR, mass and NMR spectroscopy.

IR spectrum showed the characteristic peaks of -OH and C=N at 3396 cm^{-1} and 1763 cm^{-1}.

^{1}H NMR showed characteristic singlet peak at 12.379 for the hydrogen of hydroxyl group. This hydroxyl hydrogen peak is more deshielded than other hydrogen. Also this ^{1}H NMR give multiplet for phenyl hydrogen at 7.3, another singlet peak at 8.033. This ^{1}H NMR also give two triplet peak at 2.93 and 2.75 and two singlet peak at 3.69 and 3.60.

^{13}C NMR gives more deshielded peak at 163.35 for the carbon which is directly attached to the hydroxyl group. Also it gives deshielded peak at 158.09 for the carbon which is attached to two adjacent nitrogen atom. It also gives other peak at 145.60, 138.57, 130.29, 129.71, 129.24, 128.75, 127.55, 122.79, 61.29, 51.42, 49.41, 26.10

Mass spectrum of the compound showed the peak at 297[M^{+}], 91 (base peak).

CHAPTER 6
CONCLUSION

Conclusion:

Several current and convergent synthetic approaches to pyridines and pyrimidines have been reported. Many of these reports proposed new modifications to existing methodologies, whereas others describe unprecedented transformations. Condensation chemistry of amine- and carbonyl-containing fragments is still common, but the current trend in pyridine and pyrimidine synthesis appears to be toward transition-metal-catalyzed processes, whether it is assembly of the pyridine ring or pyrimidine ring or substituent modification by cross-coupling chemistry. Pyridine and pyrimidine derivatives are very important chemicals with various biological application. With changing substituents on the pyridine and pyrimidine moiety the biological targets vary from microbial diseased to viral problems and variety of cancerous cells.

In our current work we synthesized new pyridine and pyrimidine based derivatives D1C1,D1C2 and 2AT22.The new synthesized compounds may be further explored for generation new compounds which have good biological application in medicinal field.

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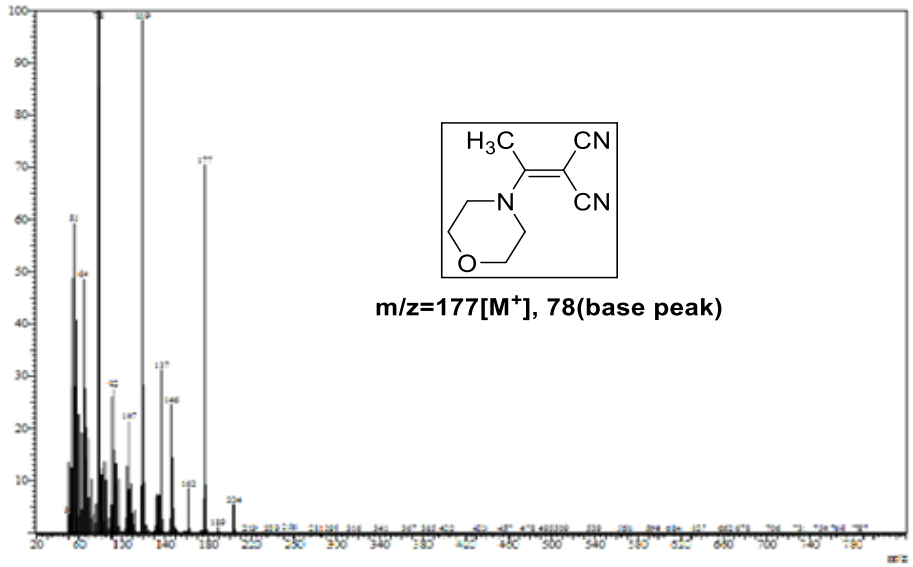
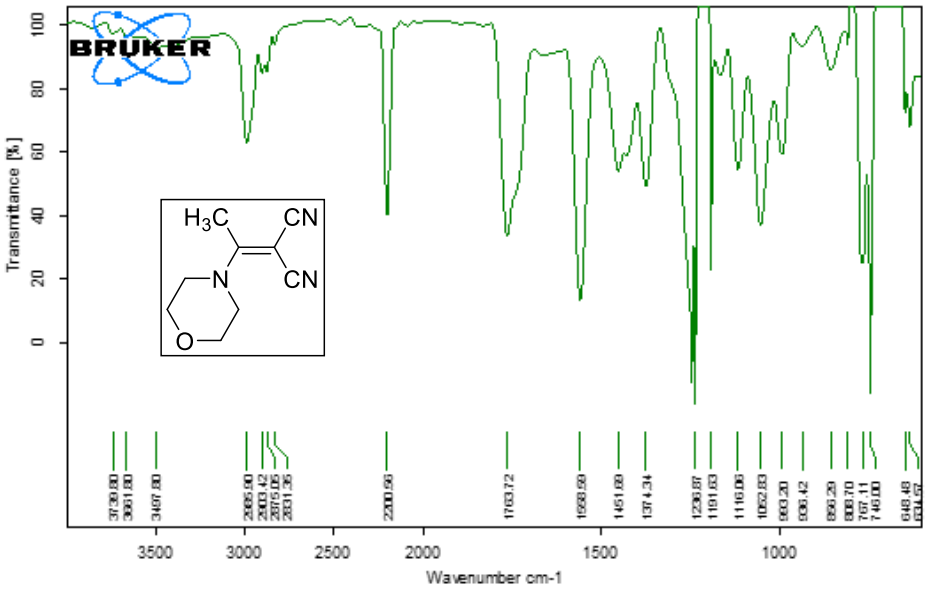
APPENDIX

Spectrul data of synthesized compounds:

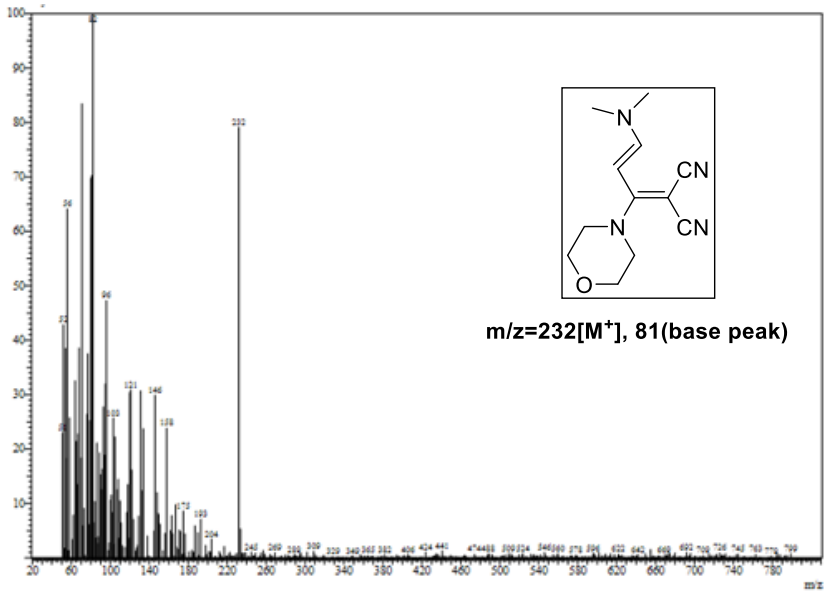


m/z=177[M$^+$], 78(base peak)

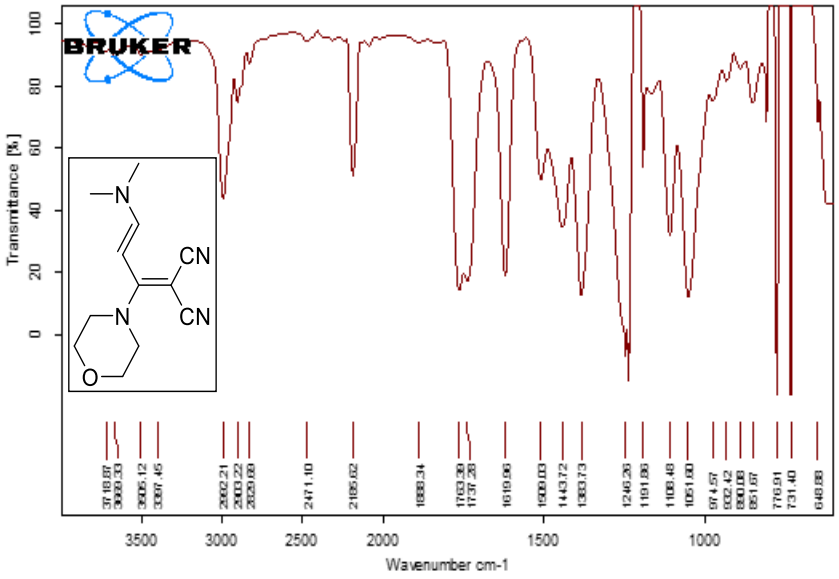
Mass spectrum of DA1



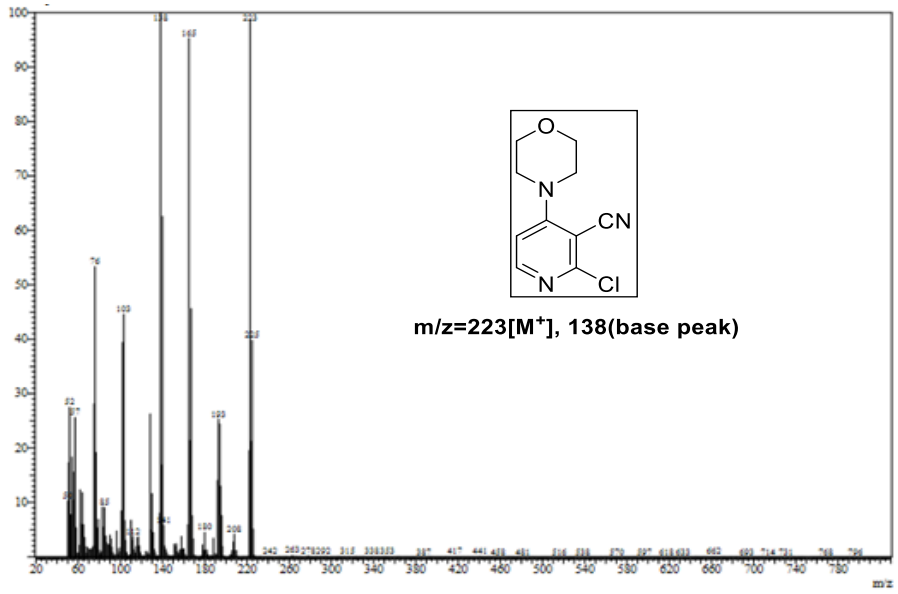
IR spectrum of DA1



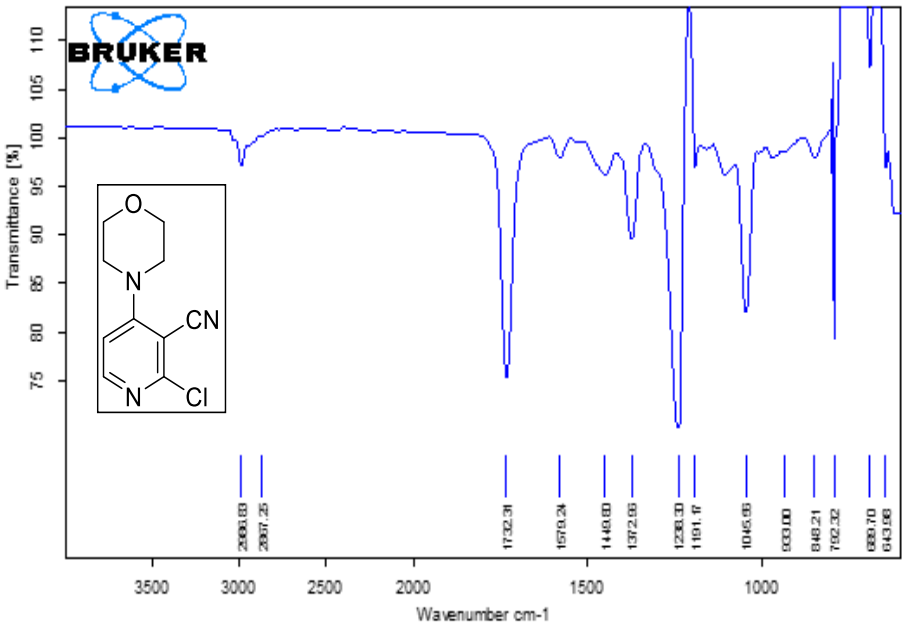
Mass spectrum of DB1



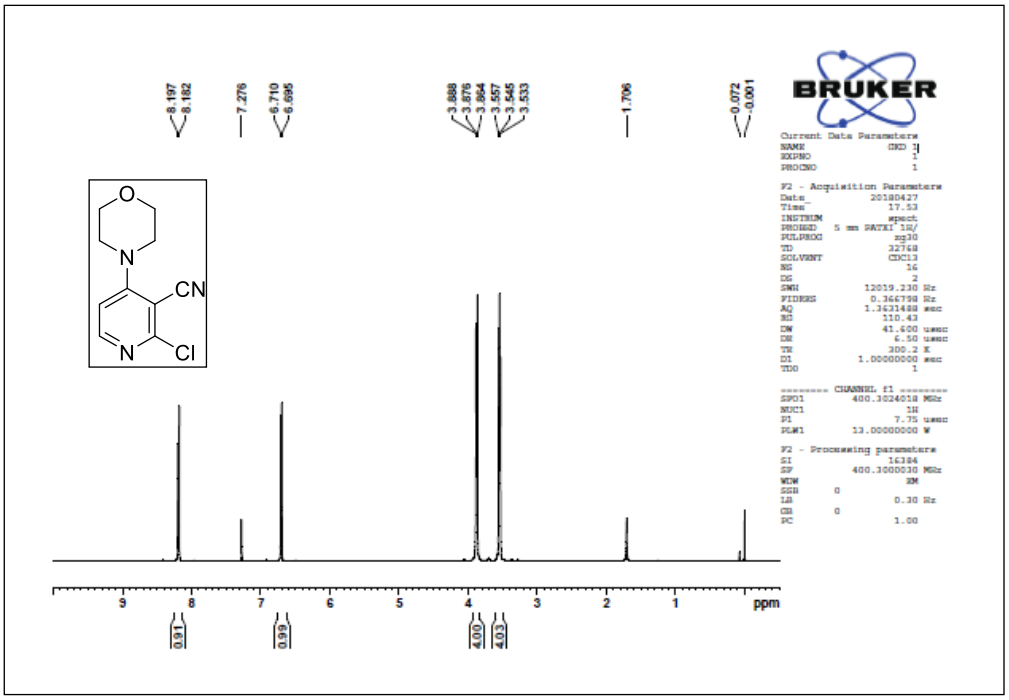
IR spectrum of DB1



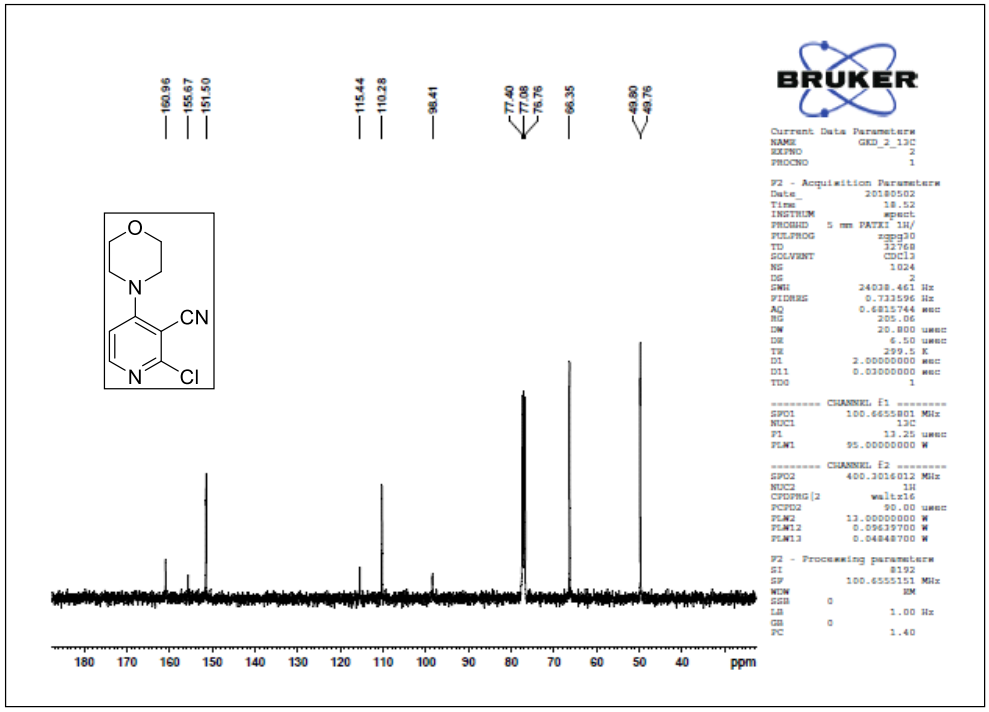
Mass spectrum of D1C1



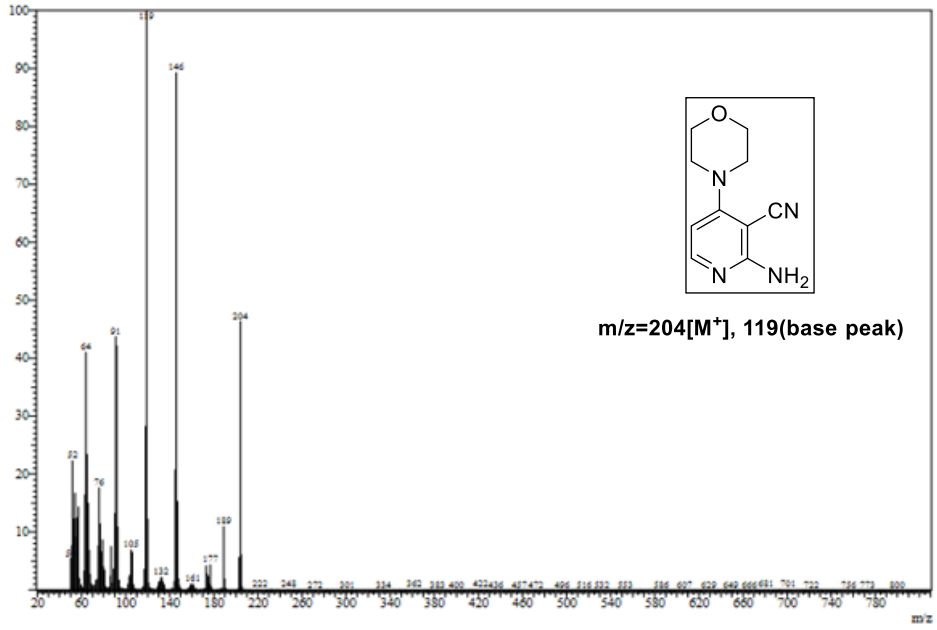
IR spectrum of D1C1



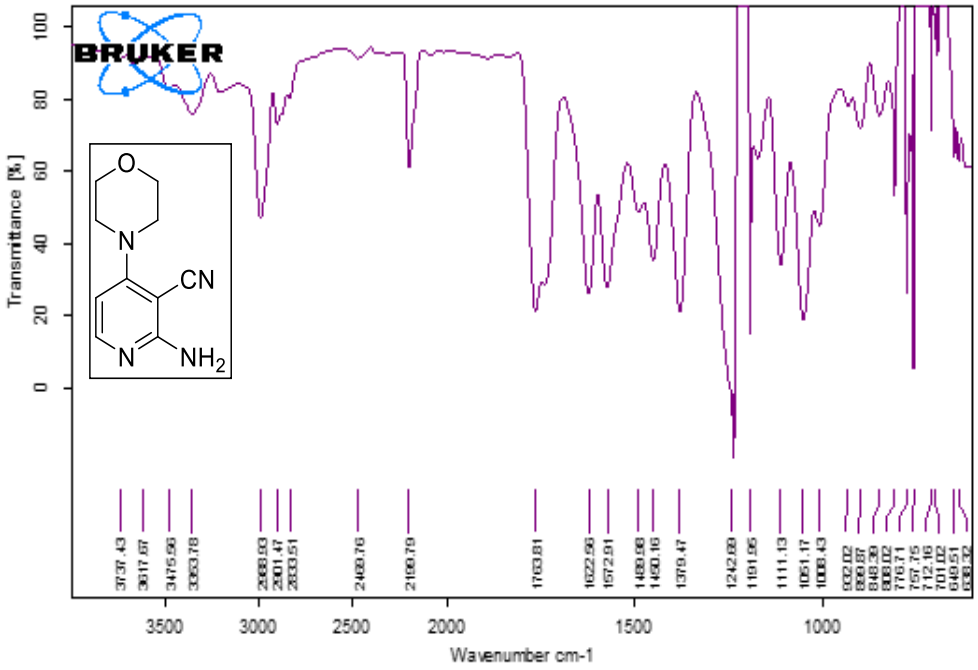
^{1}H NMR of D1C1



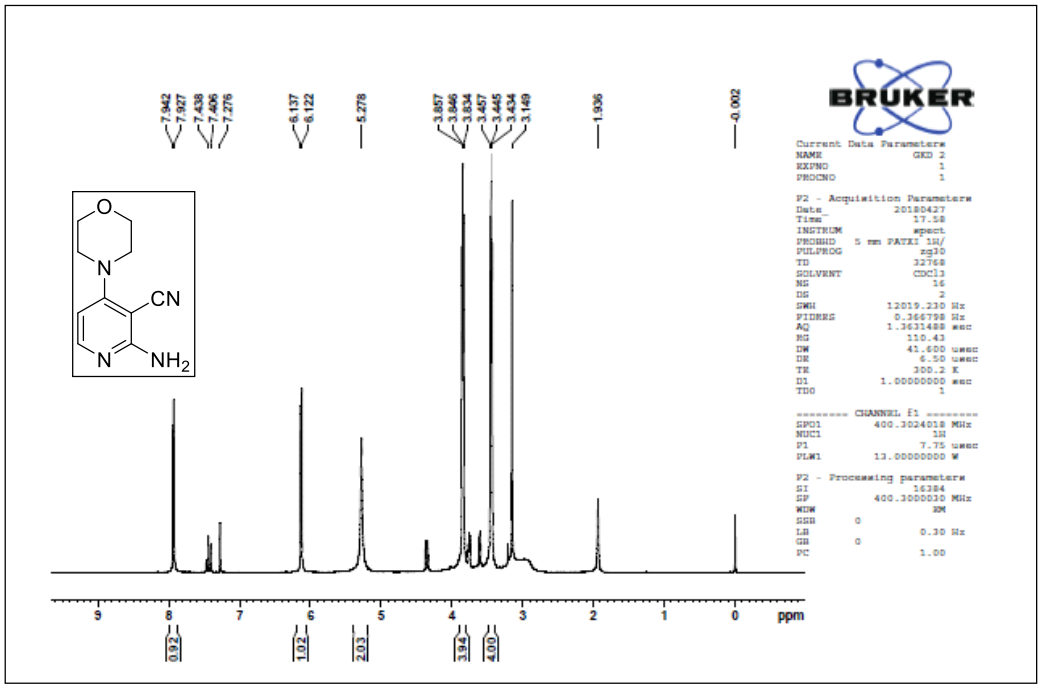
^{13}C NMR of D1C1



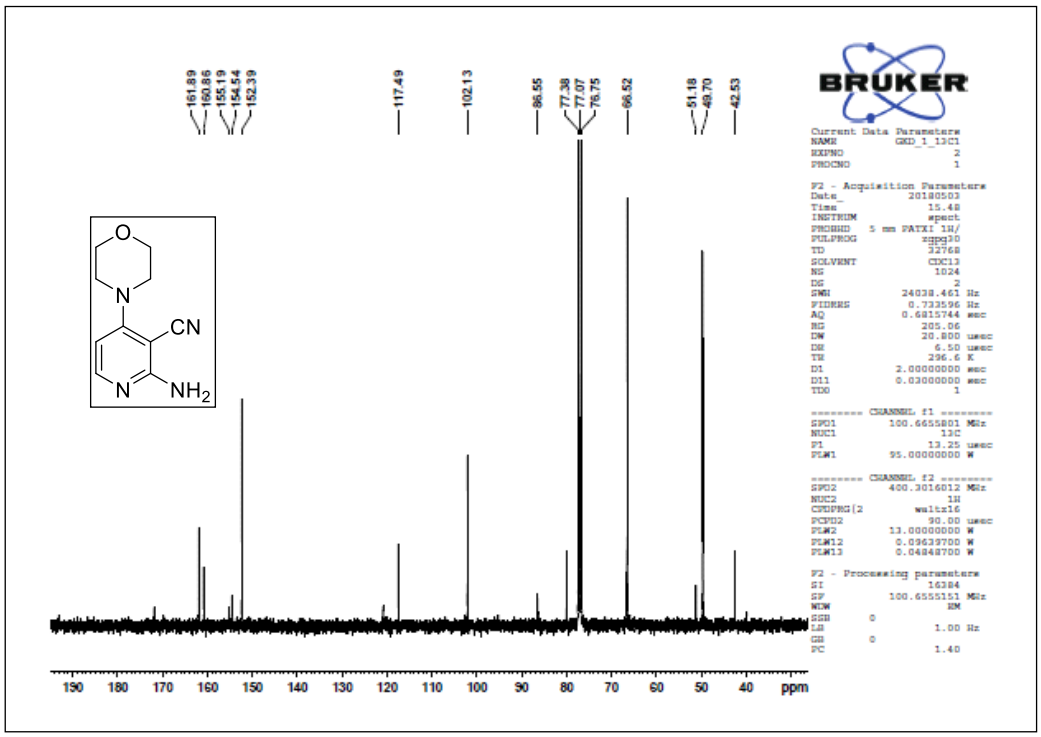
Mass spectrum of D1C2



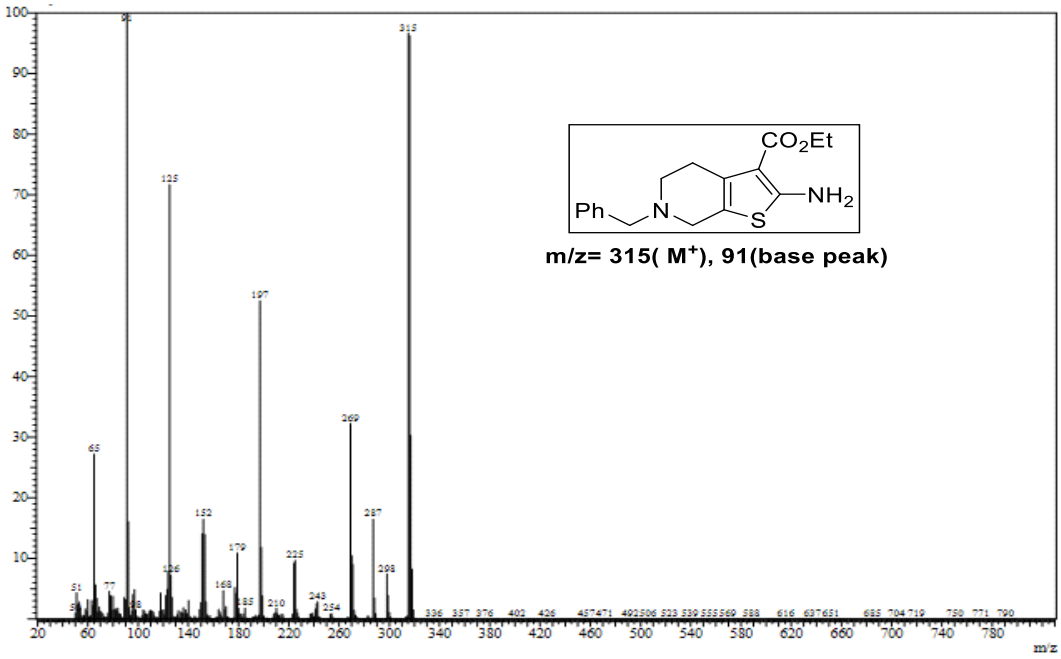
IR spectrum of D1C2



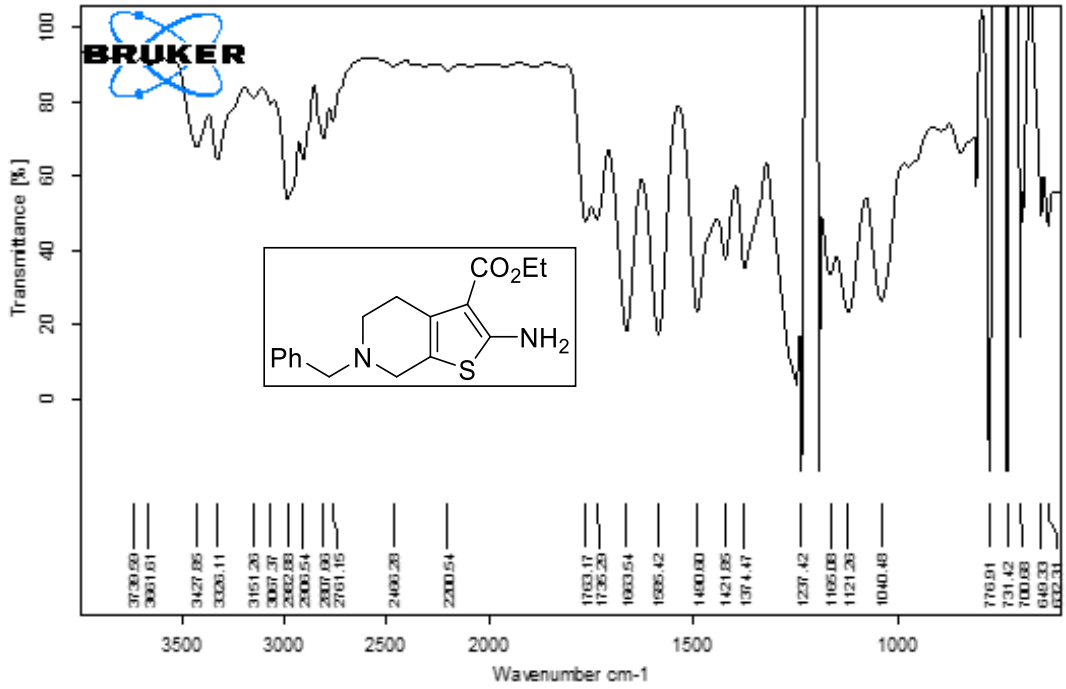
^{1}H NMR of D1C2



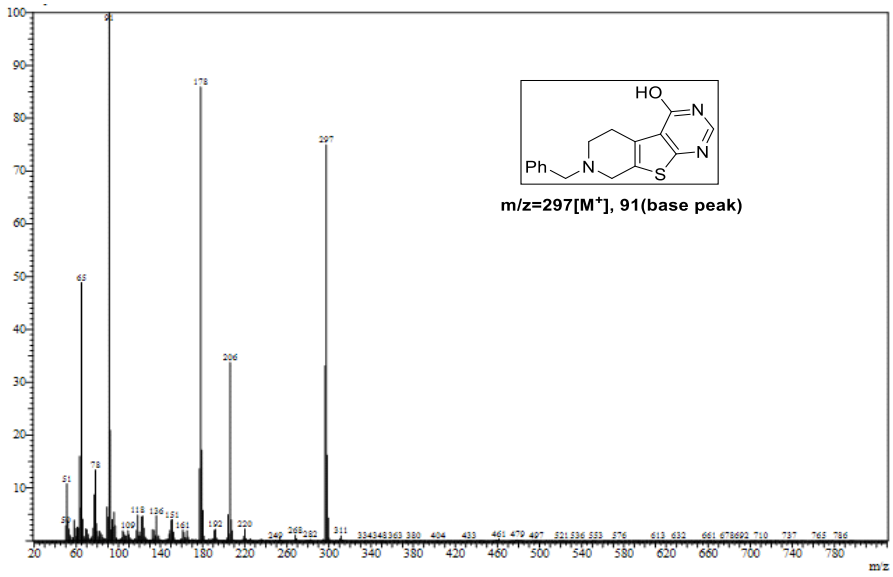
`^{13}C NMR of D1



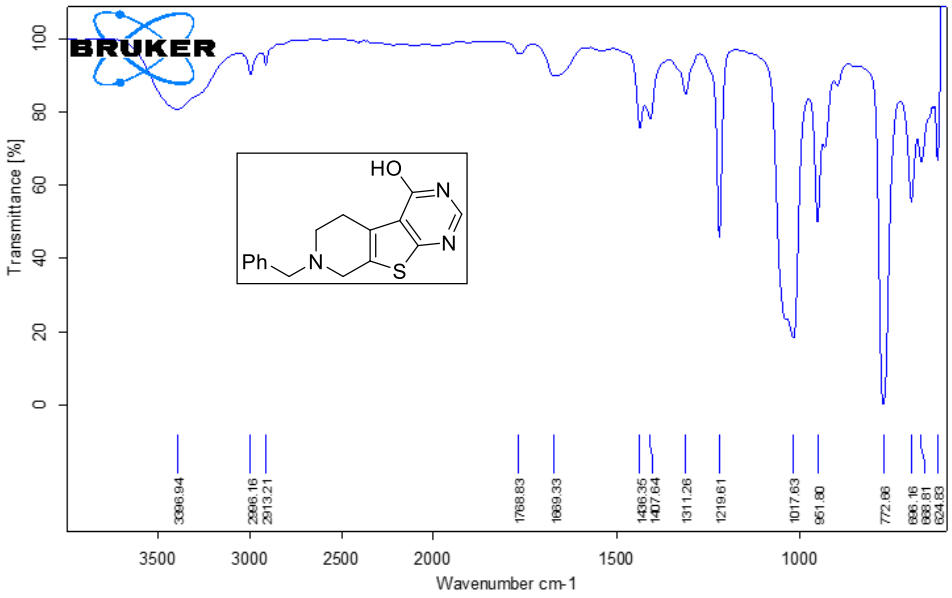
Mass spectrum of 2AT2



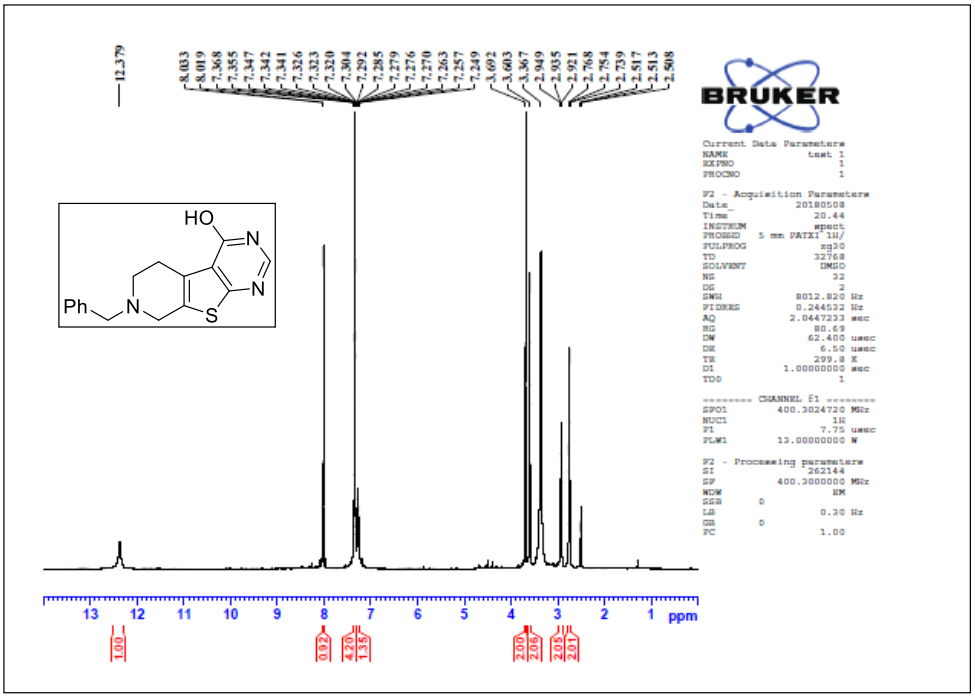
IR spectrum of 2AT2



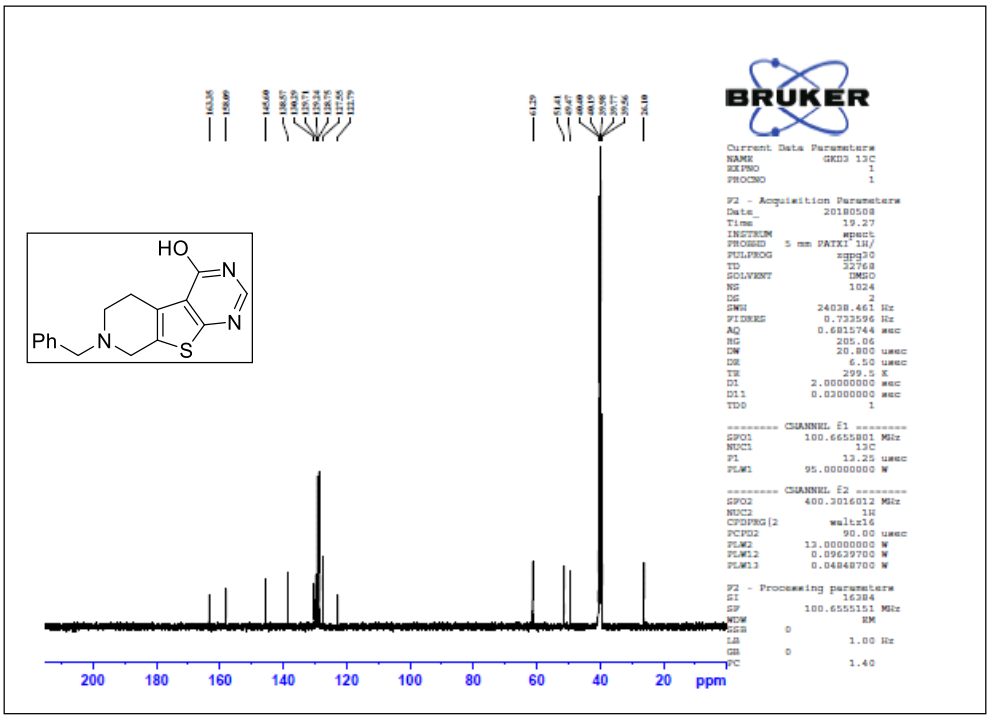
IR spectrum of 2AT22



IR spectrum of 2AT22



^{1}H NMR of 2AT22



^{13}C NMR of 2AT22