SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY OF FUNCTIONALIZED PYRIDO[1,2- a]PYRIMIDIN-2-ONES

By

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A Thesis submitted to Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore-641043

In partial fulfilment of the requirements for the degree of

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in

Chemistry

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CERTIFICATE

CERTIFICATE

This is to certify that the thesis entitled "**Synthesis, Reactions and Biological Activity of Functionalized Pyrido[1,2-a]pyrimidin-2-ones**" submitted to the Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for the award of **Doctor of Philosophy in Chemistry,** is a record of original research work done by **V.SHARULATHA,** during the period of her study in the Department of Chemistry, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, under my supervision and guidance and the thesis has not formed the basis for the award of any Degree/ Diploma/ Associateship/ Fellowship or other similar title to any candidate of any University and it represents entirely an independent work on the part of the candidate.

R.

Signature of the Head
of the Department

S. Sivakamasundari

Signature of the Guide

Parvatham R

Signature of the Dean

DECLARATION

DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Synthesis, Reactions and Biological Activity of Functionalized Pyrido[1,2-a]pyrimidin-2-ones"** submitted to the Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, for the award of **Doctor of Philosophy in Chemistry,** is a record of original research work done by me under the supervision and guidance of **Dr. (Tmt.) S. SIVAKAMASUNDARI, M.Sc., M.Phil., Ph.D., former Dean, Faculty of Science, Professor and Head, Department of Chemistry,** Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore and that it has not formed the basis for the award of any Degree/ Diploma/ Associateship/ Fellowship of any other University or Institution.

Signature of the Candidate

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ABBREVIATIONS

H_2SO_4 - Sulphuric acid

Conc - Concentration

h - hours

IR - Infra red

GC-MS - Gas Chromatography Mass Spectrometry

m/z - mass - to- charge ratio

KBr - Potassium bromide

^{1}H NMR - Proton Nuclear Magnetic Resonance

^{13}C NMR - Carbon Nuclear Magnetic Resonance

$CDCl_3$ - Deuteriated chloroform

DMSO – d_6 - Deuteriated Dimethyl sulfoxide

MeOD - Deuteriated methanol

ppm - Parts per million

TLC - Thin Layer Chromatography

NH_4OAc - Ammonium acetate

Pet-ether - Petroleum ether

EtOH - Ethanol

rt - Room temperature

PPA - Polyphosphoric acid

$POCl_3$ - Phosphorous oxy chloride

TBAB - Tertiary butyl ammonium bromide

g - Grams

mM - milli mole

THF - Tetrahydro furan

SDS - Sodium dodecyl sulfate

$NaBH_4$ - Sodium borohydride

$LiAlH_4$ - Lithium aluminium hydride

P_4S_{10} - Phosphorous penta sulphide

MHz - Mega hertz

D_2O - Deuteriated water

NH_4Cl - Ammonium chloride

MeI - Methyl iodide

COSY - H-H correlation spectroscopy

Dept - Distortion-less Enhancement by polarization Transfer

HETCOR - Heteronuclear Correlation spectroscopy

HMBC - Heteronuclear Multiple Quantum
Correlation

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INTRODUCTION

1. INTRODUCTION

Organic chemistry, the chemistry of carbon compounds is associated with nearly every aspect of our lives including life itself. Nature is endowed with diverse organic molecules. Human body is largely composed of organic molecules, the proteins, the lipids, DNA are all organic compounds. The human body is regulated and defended by complex organic compounds. Chemists have learned to synthesize many of these complex molecules. The synthetic products serve as drugs, medicines, plastics, pesticides, paints and fibers. Many of the most important advances in medicine area are actually advances in organic chemistry. New synthetic drugs are developed to combat disease and new polymers are moulded to replace failing organs.

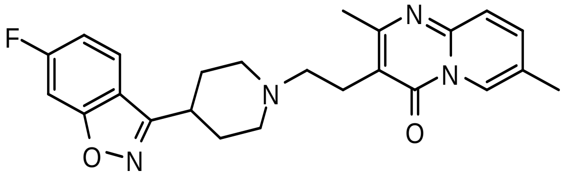
Part of the charm of synthetic organic chemistry derives from the vastness of the intellectual landscape along several dimensions. First there is the infinite variety and number of possible target structures that lurk in darkness, waiting to be made.

Heterocyclic chemistry is of prime importance as a sub-discipline of Organic Chemistry, as millions of heterocyclic compounds are known, with more, being synthesized regularly. Hundreds and thousands of natural products and pharmaceutical active ingredients contain heterocycles as central building blocks. They are present in many biologically important molecules such as amino acids, nucleic acids and hormones. They are also indispensable components of pharmaceuticals and therapeutic drugs; the most potent natural compounds, the alkaloids, are heterocycles. The chemistry of heterocyclic compounds and methods for their synthesis form the back bone of modern medicinal chemical and pharmaceutical research.

Nitrogen hetero cycles of different ring sizes with different substitution patterns embedded in various molecular frame works constitute extremely important structural class in the search for bioactivity. Examples for such systems are quinolines, naphthyridines, pyrimidines, pyrido pyrimidines etc.

The bridgehead nitrogen hetero cycles are an important class of hetrocyclic compounds, because of their wide use in medicinal and agro chemistry as scaffolds for active agents such as antiviral, antiulcer, anti malarial, antifungal, herbicidal, anti leprotic and immune suppressive agents. Saturated and partially saturated bicyclic 6-6 systems with one ring junction and one extra nitrogen atom viz pyrido[1,2-a] pyrimidines, pyrimido[1,2-a] pyrimidines and pyrazino[1,2-a] pyrimidines occur in many natural and biologically active compounds.

Pyrido[1,2-a] pyrimidine represents a simple bicyclic ring system that contains a nitrogen-bridgehead condensed pyrimidine moiety. Pyrido[1,2-a] pyrimidine core had been a successful motif for the development of biologically interesting molecules including risperidone **1** and paliperidone **2** antipsychotic agents, metreperone **3** a selective 5HT_2 receptor antagonist and lusaperidone **4** an antidepressant **(Alan R. Katritzky 2004 and Koilpillai Joseph et al, 2011).**



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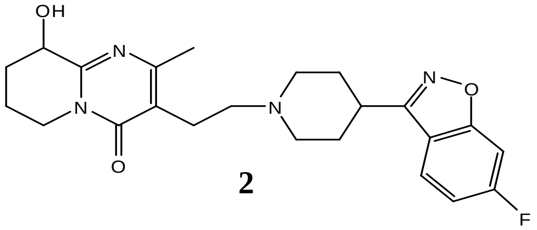

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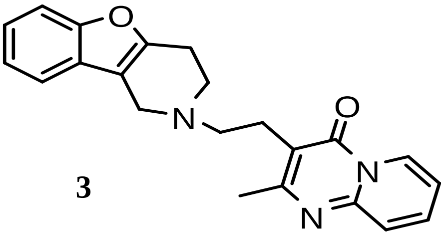

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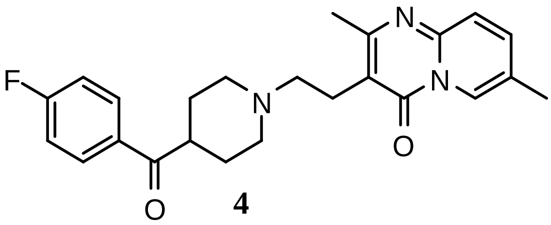

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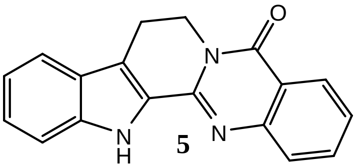
Pyrido[1,2-a]pyrimidine core also form a part of several natural products. For eg., Rutecarpine **5** contains the pyrido[1,2-a]pyrimidine moiety.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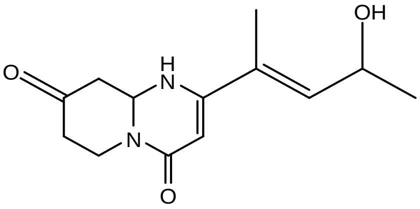
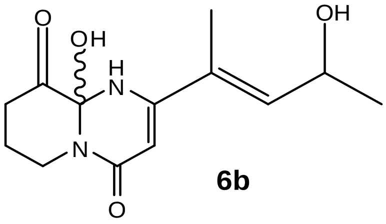
Recently, three new naturally occurring bicyclic alkaloids, jenamidines **6a, 6b** and **6c**, were discovered and isolated from the culture broth of Streptomyces sp. (strain HKI0297) via the chemical screening approach by **Jin-Feng Hua et al, 2003.** The jenamidines have an unusual octahydro-pyrido[1,2-a]pyrimidine skeleton. Jenamidine **6a** showed antiproliferative effects against the chronic myeloid leukaemic cell line K-562.


6a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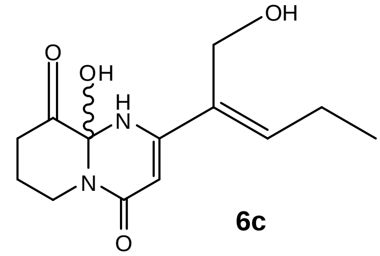
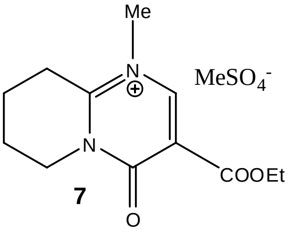

6c

The analgesic rimazolium methyl sulphate a quaternary ester of pyrido [1,2-a] pyrimidin4-one **7** was introduced into the drug market in second half of 1970’s. It was successfully applied for the treatment of patients with postoperative pain, and rheumatic diseases **(Istvan Hermecz et al, 1988).**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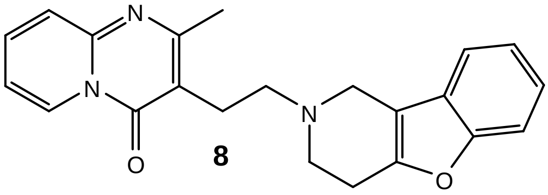
The combination of rimazolium with either morphine or azidomorphine prevented the development of tolerance to the narcotic analgesics in cancer patients. The azidomorphine-rimazolium combination provided complete pain relief, without the development of addiction and or tolerance.

Radio labeled 2-methyl-3-[2-(1,2,3,4-tetrahydrobenzo[4,5]furo[3,2-c]pyridin-2-yl)ethyl]-4H-pyrido[1,2-a]pyrimidin-4-one **8** was prepared and evaluated as a potential positron emission tomography (PET) ligand for studying central alpha(2)-adrenoceptor antagonist by **Van der Mey et al, 2006.**



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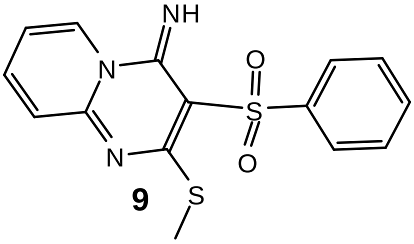
(E)-3-(Benzenesulfonyl)-2-(methylsulfanyl)pyrido[1,2-a]pyrimidin-4-ylidenamine **9** was found to be a potent and selective 5-HT(6) antagonist **(Wu et al, 2003).**



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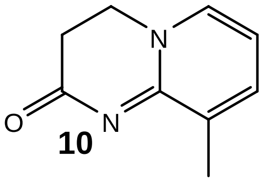

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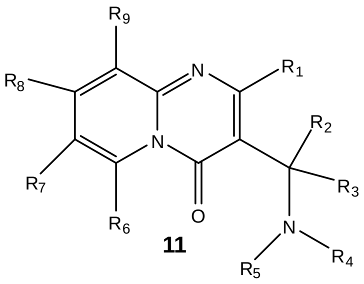
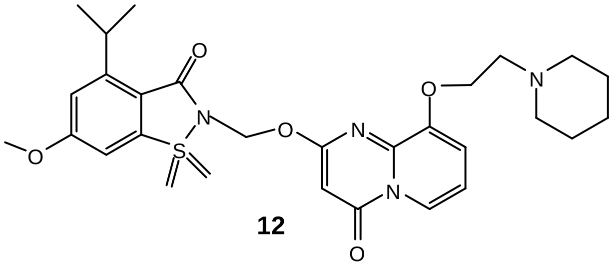
9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one **10** along with 2-bromo-1-ethylpyridinium tetrafluoroborate, 2-(2-Aminoethyl)-1-methyl pyrrolidine and N-(3-aminopropyl)pyrrolidine (NAPP) were found to be selective and sensitive derivatization reagents for carboxylic acid by high-performance liquid chromatography (HPLC) with electrogenerated chemiluminescence detection using tris(2,2'-bipyridine)ruthenium(II) (**Morita et al, 2002).**

(9-[4-acetyl-3-hydroxy-2-n-propylphenoxy) methyl]-3-(1H-tetrazol-5-yl)-4H-pyrido [1,2-a] pyrimidin-4-one) was found to contain anti-allergic property **(Hamasaki et al, 2000).** Pyridino[1,2-a]pyrimidinyl compounds of the structure **11** had been patented as anticancer agent **(Weibo Wang et al, 2011).** 2-(9-(2-Piperidinoethoxy)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yloxymethyl)-4-(1-methyl ethyl)-6-methoxy-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (SSR69071), **12** was found to be a novel, orally active elastase inhibitor **(Zolta'N Kapui et al, 2003).**

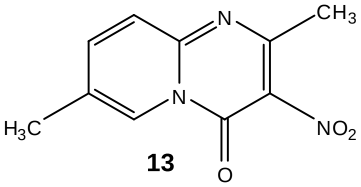


11



12

Anti-histaminic, anti-inflammatory and bronchorelaxant activities of 2, 7-dimethyl-3-nitro-4H-pyrido [1,2-a] pyrimidine-4-one **13** were investigated by **Youssouf et al, 2008**. **Giorgio Roma et al, 2000** described, 2-2-piperazinyl04H-pyrido[1,2-a] pyrimidine-4-one **14** as invitro inhibitor of human platelet aggregation which specifically inhibited the activity of high affinity CAMP phosphodiesterase.



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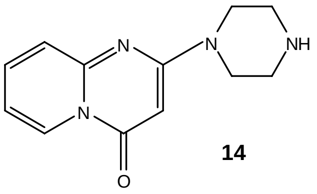

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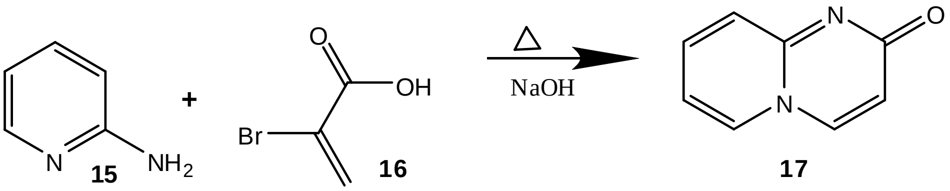
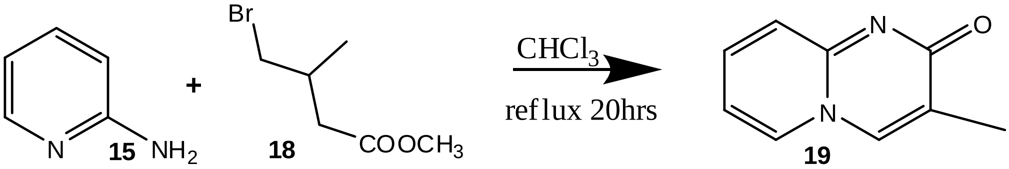
1.1 Synthesis of 2H -pyrido[1,2-a] pyrimidin-2-ones

Over the last 84 years and from the time when Tschitschibabin prepared 2-hydroxy-4H–pyrido[1,2-a] pyrimidine-2,4 dione under the name of malonyl α amino pyridine, many synthetic reaction studies had been carried out to deal with its derivatives.

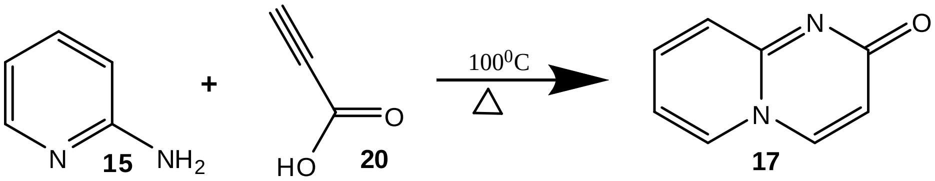
Some of the earlier methods to synthesize 2H–pyrido[1,2-a]pyrimidin-2-ones include the reaction of 2-amino pyridine **15** with α–bromo acrylic acid **16**, β bromopropionic ester **18** and propiolic acid **20**.



(Roger Adams et al, 1952)

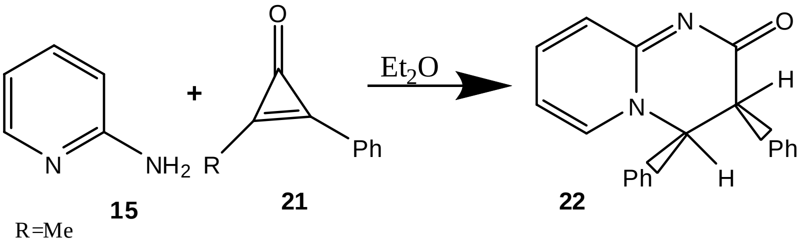


(Krishnan 1958)

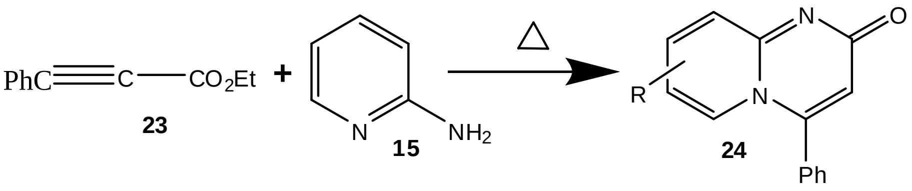


(Irwin J. Pachter 1961)

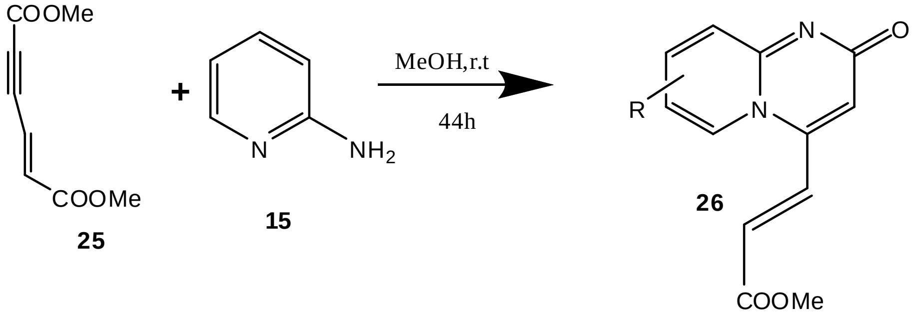
Cyclo addition reaction of methylphenylcyclopropenone **21** with 2-aminopyridine **15** in ether at room temperature yielded cis-3,4-dihydro-3-methyl-4-phenyl-2H-pyrido[1,2-a]pyrimidin-2-one **22**. The reaction time varied between 17 hrs to 22 days **(Albert Kascheres et al, 1976).**



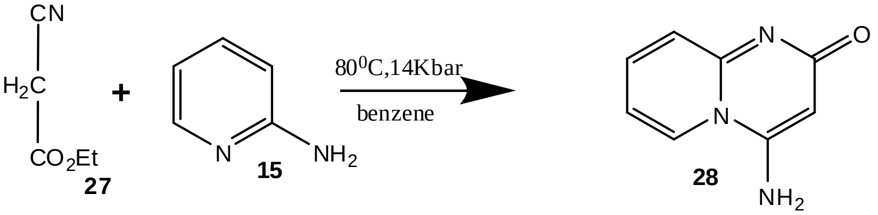
Reaction of ethyl phenylpropiolate **23** with 2-aminopyridine **15** at 130^0C – 140^0C yielded 2H-pyrido[1,2-a] pyrimidin-2-ones **24** **(Hikmat At-Jallo et al, 1978a).**



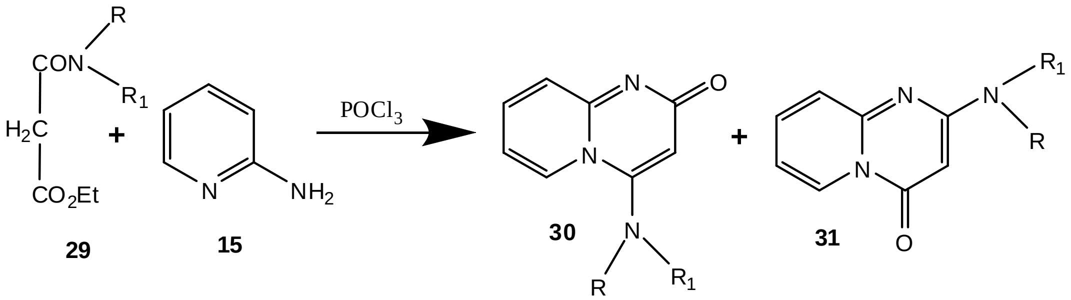
When dimethyl hex-2-en-4-yne-1,6-dioate a dimerized product of methyl propiolate **25**, was reacted with 2-aminopyridine **15** in refluxing methanol for 44 hours (E)-3-(2-oxo-2H-pyrido[1,2-a]pyrimidin-4-yl)prop-2-enoate **26** was obtained, but the product could not be purified either by chromatography or by recrystallization **(Acheson et al, 1982).**



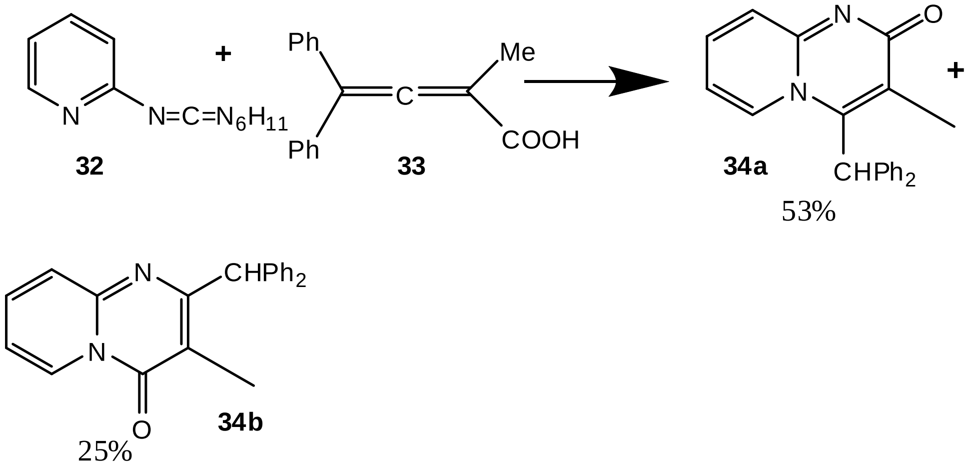
4-amino-2H-pyrido[1,2-a]pyrimidin-2-ones **28** were obtained by the reaction of 2-aminopyridines **15** with ethyl cyanoacetate **27** in benzene at 80^{0}C under 14 K bar pressure for 5 hours in 40 -65% yield **(Dorokhov et al, 1989).**



In some reactions, the isomeric 2-oxo-2H and 4-oxo-4H-pyrido[1,2-a]pyrimidines are simultaneously formed. Reaction of 2-aminopyridines and N,N-disubstituted malonamates **29** afforded mixtures of 4amino-2-oxo-2H- **30** and 4amino-4-oxo-4H-pyrido[1,2-a]pyrimidines **31** in boiling 1,2-dichloroethane with phosphoryl chloride **(Roma et al, 1987).**



The reaction of N-cyclohexyl-1N-(2-pyridyl)carbodiimide **32** and the allenic acid **33** in dry tetrahydrofuran at ambient temperature for 3days afforded a 2:1 mixture of isomeric 2-oxo-2H- **34a** and 4-oxo-4H-pyrido[1,2-a]pyrimidines **34b (Trifonov et al, 1992).**



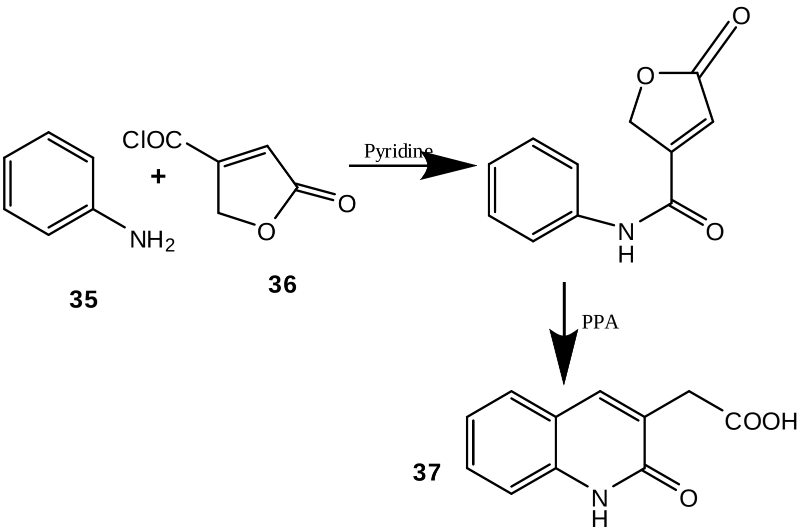
From the survey of literature, it was realized that compounds containing pyrido[1,2-a]pyrimidine moiety displayed a broad spectrum of pharmacological properties. Also it was noticed that heterocycles with pyrido[1,2-a]pyrimidine systems are of considerable contemporary interest since this structural framework is also present in natural products displaying remarkable pharmacological properties. The distinguished and unique chemical properties and biological applications of pyrido[1,2-a] pyrimidinones evoked an interest for the synthesis of this moiety.

A number of methods have been accomplished to synthesize pyrido[1,2-a] pyrimidines-4-one but only a few methods had been reported for the synthesis its regio isomer, pyrido[1,2-a] pyrimidines-2-one. The drawback of these methods includes.

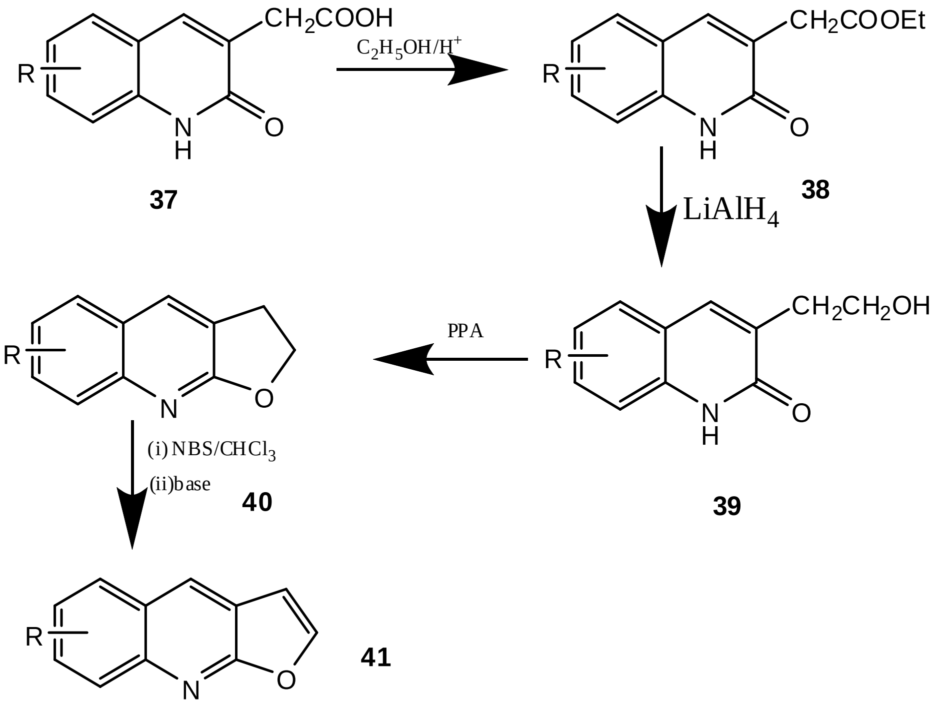
- The need to use high temperatures and pressure,
- Use of acid catalysts,
- Lack of regio control in the reaction conditions,
- Low yields and
- Formation of the significant amount of byproducts.

Hence it has been attempted to develop simple and high yielding synthetic routes for these biologically diverse compounds from readily available reagents.

Quinolone acetic acids **37** were versatile precursors and valuable intermediates for the synthesis of furo **41**, thieno **43** and pyrrolo **46** quinolines. The quinolone acetic acids were obtained by an elegant and novel method based on the use of aniline and aconic acid, a five membered heterocyclic synthon as starting points **(Shanmugam et al, 1973).**

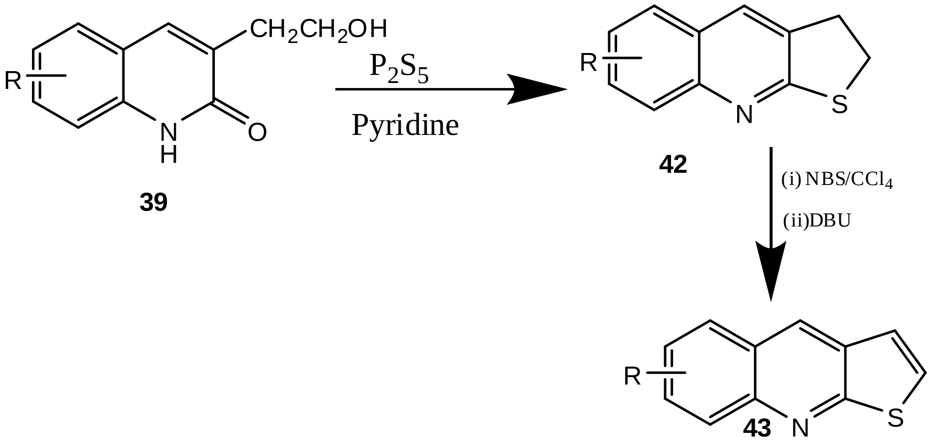


Appropriately substituted 2-quinolone-3-acetic acids **37** had been employed as intermediates by **Gnanasekaran et al, 1977** for the synthesis of furo quinoline alkaloid **41** which occurs in Rutacceae family. The esters of quinolone acetic acids **38** were reduced with lithium aluminium hydride and the resulting alcohols **39** were cyclized using PPA to give the corresponding dihydrofuroquinolines **40** and subsequent treatment of the resulting 3-bromo derivative with a base like triethylamine or more effectively with DBU gave the corresponding furo(2,3-b) quinolines **41**.



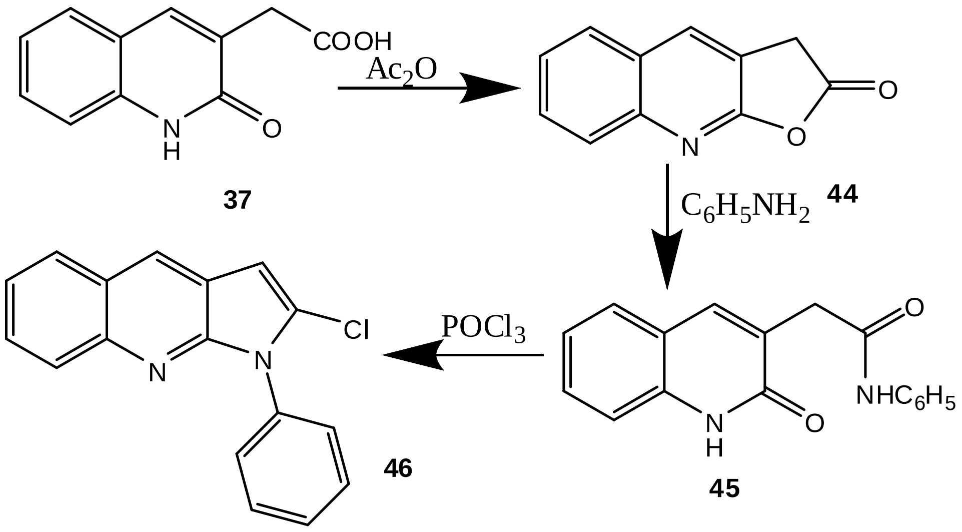
37 **38** **39** **40** **41**

The alcohol **39** derived from the quinolone acid when heated with phosphorous pentasulfide in pyridine solution, furnished the 2,3-dihydro thieno(2,3-b) quinoline **42** which was then converted into thieno(2,3-b)-quinoline **43** by allylic bromination followed by dehydrobromination with DBU **(Shanmugam et al, 1976).**

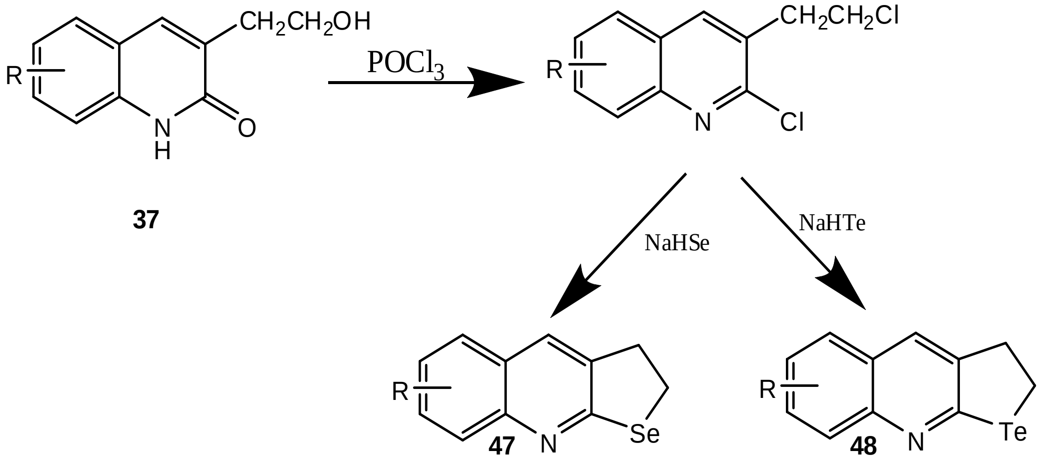


39 **42** **43**

Pyrrolo quinolines were obtained from 2-quinolone-3-acetic acids by the following scheme **(Sivakamasundari 1980).**



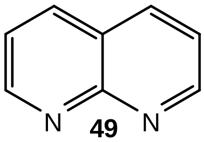
Utilizing 3-(2-hydroxy ethyl)-quinolin-2(1H) ones as precursors**, Shanmugam et al, 1977a and Ramasamy et al, 1978**, realized the convenient synthesis of selenolo **47** and tellurolo (2,3-b)quinolines **48**.



2-amino pyridine compounds are a class of compounds, well known for a long time and still continue to be the object of considerable interest, mainly due to their application in different fields. The primary use of 2-aminopyridine is as intermediate in the manufacture of pharmaceuticals.

Hence it was considered to utilize 2-amino pyridine as starting point instead of aniline and to subsequently study the condensation of various 2-amino pyridines with aconic acid.

Different regio orientation of the cyclo condensation in the reaction with α amino derivatives of the nitrogen heterocyles like 2-aminopyridine due to the possibility of attack both at the “C” atom and at the endo hetero atom of the initial hetroarylamine makes it possible to synthesize 1,8 naphthyridines **49** and pyrido pyrimidines **50**. Literature survey showed that 2-amino pyridines and its derivatives with different acylating and alkylating agents yielded pyrido pyrimidines as the major products.



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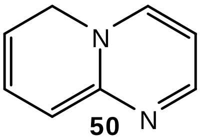
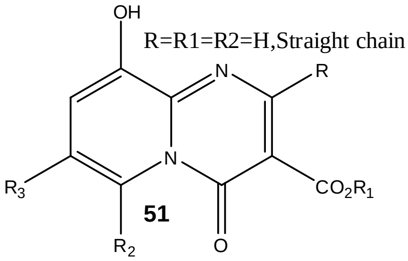


50

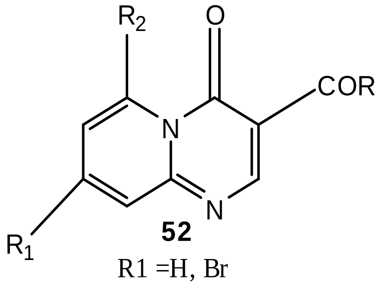
Recent crystallographic and molecular modeling studies have shown that carboxylic acid inhibitors bind to the active site of ALR2 with the acidic function underlying Y48H110 and W111 which are the three key residues in binding and catalysis. 9-substituted-4-oxopyrido[1,2-a]pyrimidine-3-carboxylic acid derivatives **51** were patented for their central nervous system depressant activity **(Yale 1976).**



51

R=R1=R2=H,Straight chain alkyl

4-oxo-4H-pyrido[1,2-a]pyrimidine-carboxylic acid derivatives **52** possessed slight hypoglycemic activity in rats **(Gupta 1971).**



52

R1 =H, Br

R2 = H,Me

The chemistry of carboxylic acids is very i

of carboxylic acid function to be transformed to different derivatives. These were the motivating factors to develop a simple and facile route for the synthesis of pyrido[1,2-a] pyrimidine acetic acids.

1.3 OBJECTIVES

In the present study, it is contemplated to develop some simple and elegant procedure for the preparation of some pyrido-pyrimidine derivatives which will give a new dimension and impetus to the proliferation of studies on this system.

With the goal of devising a milder and more general method of synthesizing functionalized pyrido[1,2-a]pyrimidin-2-ones the following objectives were set forth

- To develop a simple method for the synthesis of pyrido pyrimidine acetic acid derivatives using aconic acid and 2-amino pyridine as starting compounds.
- To characterize the compounds with IR, NMR and Mass Spectra.
- To further confirm the structure using COSY, HETCOR, & HMBC studies.
- To carry out the following reactions and to characterize the product obtained.
    - Reaction with PPA
    - Reaction with acetic acid
    - Reaction with trifluoro acetic acid
    - Reduction with $LiAlH_4$
    - Reduction with $NaBH_4$
- To prepare some of the derivatives and characterize them
    - Preparation of amides.
    - Preparation of thiadiazole derivatives
    - Thione derivatives
    - Dithiol ester derivatives
- To carry out anti cancer and anti bacterial studies for some of the synthesized compounds.
- To calculate ClogP values and drug likeliness properties using Chemdraw ultra 10.0, OSIRIS and Molinspiration softwares.

REVIEW OF LITERATURE

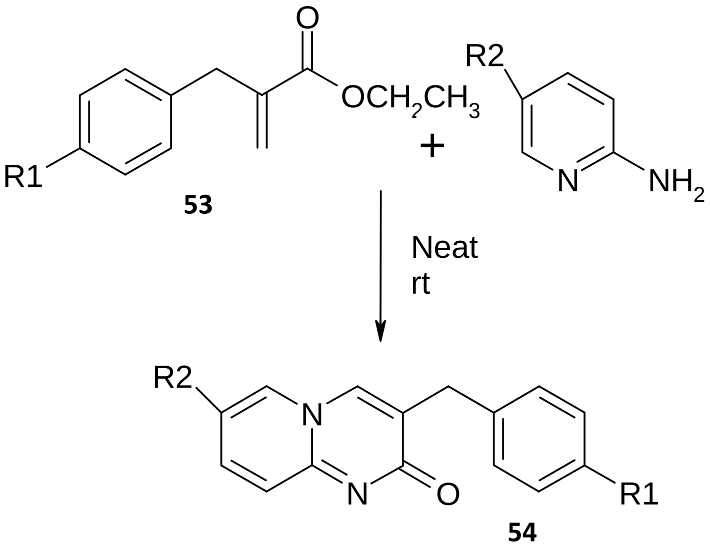
2. REVIEW OF LITERATURE

A research work is a gradual process and systematic unfoldment of important existing concepts, which have been dealt with the experiments by experts and science scholars. The literature of past finding and studies is essential and indispensable for further experimentation and research work where the discovery of new concepts is an extension of existing concepts. So the present work is reviewed under the following headings.

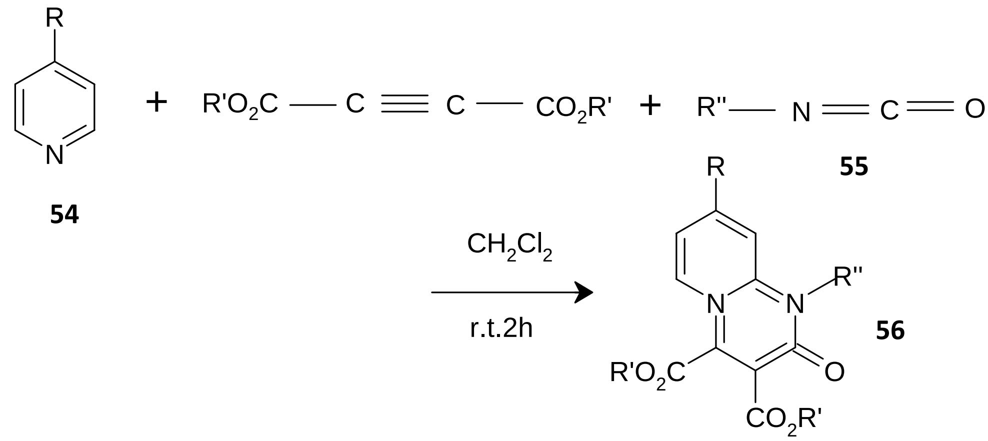
- Synthesis of 2-oxo-2H-pyrido[1,2-a]pyrimidinone
- Synthesis of 4-oxo-4H-pyrido[1,2-a]pyrimidinone and its application
- Reactions of 4-oxo-4H-pyrido[1,2-a]pyrimidinones
- Physicochemical properties and structural studies
- Pyrido-diazepines

2.1 Synthesis of 2-oxo-2H-pyrido[1,2-a]pyrimidinone

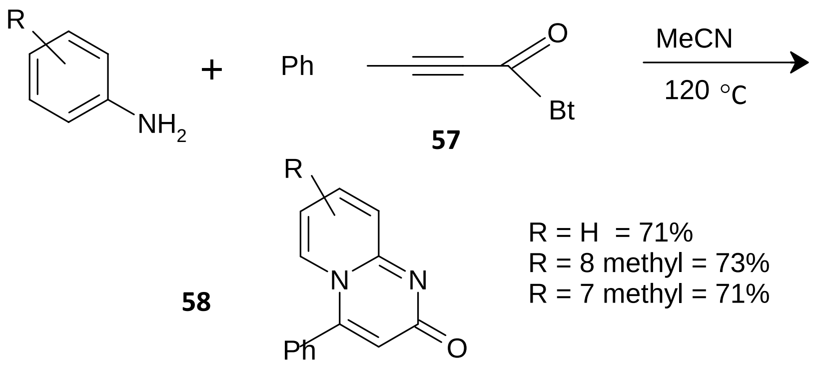
A facile one pot transformation of Baylis Hillman acetates **53** to pyrido[1,2-a]pyrimidin-2-ones **54** by reaction with 2-amino pyridine in a total solvent-free protocol was illustrated by **Sreevani et al, 2011.**



Mehdi Adib et al, (2004) reported that pyridines **54** reacted. Smoothly with dialkyl acetylene dicarboxylates in the presence of isocyanates **55** in dry dichloro methane at ambient temperature to produce dialkyl 2-oxo 1,9a dihydro –2H-Pyrido [1,2-a] pyrimidine **56** in excellent yields.

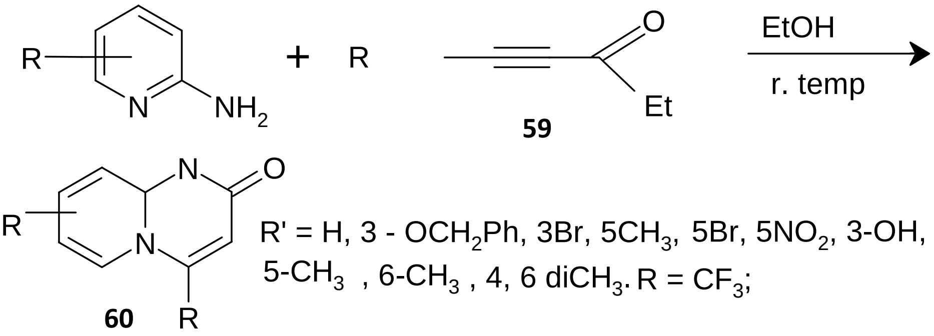


Alan Katritzky et al, (2004) reported the synthesis of pyrido [1, 2-a] pyrimidin-2-ones **58** from a novel 1, 3 bis-electrophilic synthons (viz) 1-benzatriazol-1-yl-3-phenylpropynone **57** and 2-aminopyridines in good yields (71-73%).



R = H = 71%
R = 8 methyl = 73%
R = 7 methyl = 71%

Geraldine Harriman et al, (2003) prepared biologically relevant 4-tri fluoromethyl pyrido [1, 2-a] pyrimidine-2-one **60** in good yields by utilizing the reaction between electron rich amino pyridines and the highly electrophilic ethyl β-trifluoromethyl-alkynoate **59** in ethanol at room temperature. The 2-amino pyridine moiety with electron withdrawing group in the 5th position viz bromo and nitro reacted very slowly to afford the desired pyrido [1, 2-a] pyrimidin-2-ones in fair yields. The reaction was assumed to proceed via Michael addition at the pyridine nitrogen followed by lactam formation involving the 2-amino group to provide pyrido [1, 2-a] pyrimidinone.

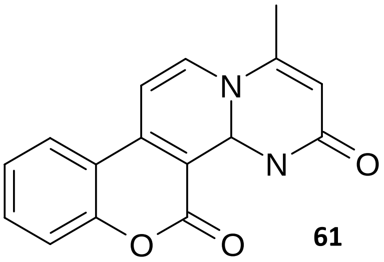


59

60

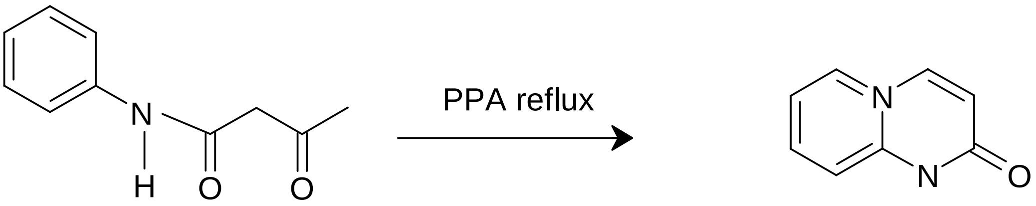
R' = H, 3 - OCH_2Ph, 3Br, $5CH_3$, 5Br, $5NO_2$, 3-OH, 5-CH_3 , 6-CH_3 , 4, 6 diCH_3. R = CF_3;

Fatima Al-Omran (2003) reported new synthetic routes for triazolopyridine, Pyridopyrimidine **61**, Pyridazine derivatives, incorporating a coumarin moiety with biological activities.



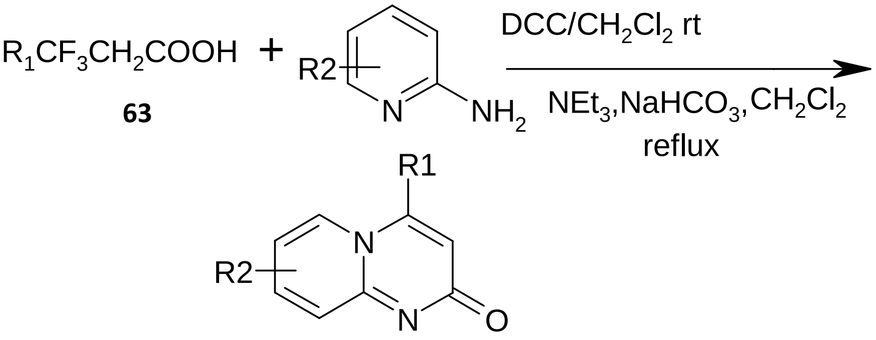
61

Suri et al, (2002) reported an unequivocal high yielding synthesis of 4-methyl-2-oxo-2(H)-pyrido[1,2-a]pyrimidines **62** by the cyclisation of N-(1,3-dioxobutyl)–2 amino pyridines / picolines / quinolines with PPA. The examination of HOMOCOR and HETCOR Spectra of the compounds revealed that C_4-Methyl has an influence on the chemical shifts of C_6 and its α proton. In all the end products, C_6-H possessed lower chemical shift in comparison to C_8. The abnormal shielding of C_6 in spite of being attached to nitrogen was attributed to peri-effect of C_4 methyl group.



62

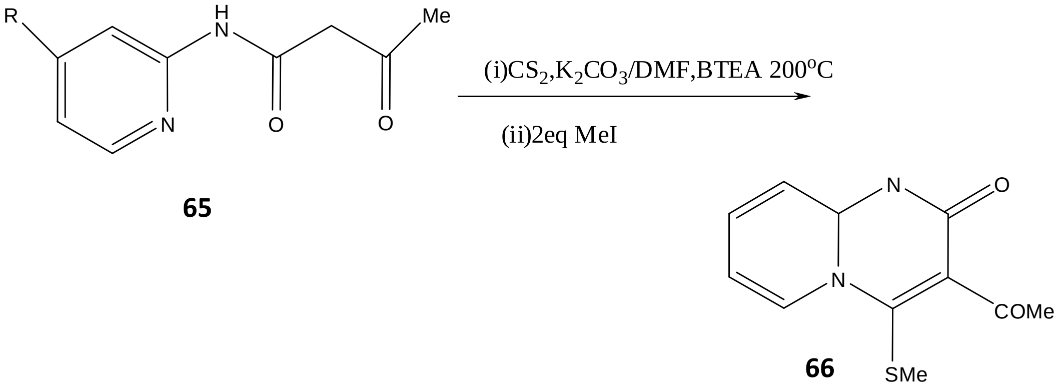
The reaction of 2-amino pyridine with 2,2-dihydropolyfluoroalkonic acids **63** in presence of DCC gave the corresponding amides which subsequently cyclised by intramolecular Micheal addition-elimination reaction amides under basic condition to yield 4-fluoroalkyl-2H-pyrido[1,2-a]pyrimidin-2-ones **64** **(LU et al, 2001).**



63

64

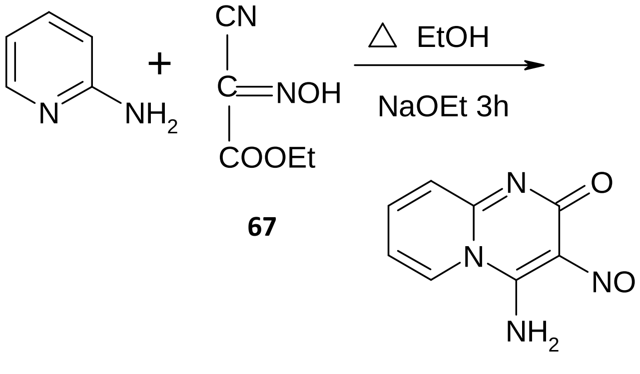
4-Methylthiopyrido[1,2-a]pyrimidin-2-one **66** was synthesized by the addition of *N*-(4-R-pyrid-2-yl)acetoacetamides **65** (R = H, Me) to CS_2 under phase-transfer conditions followed by the alkylation of the reaction products with Mel. The molecular structure of 3-acetyl-4-methylthiopyrido[1,2-α]pyrimidin-2-one is established by X-ray analysis **(Cherkasova et al, 1996).**



65

66

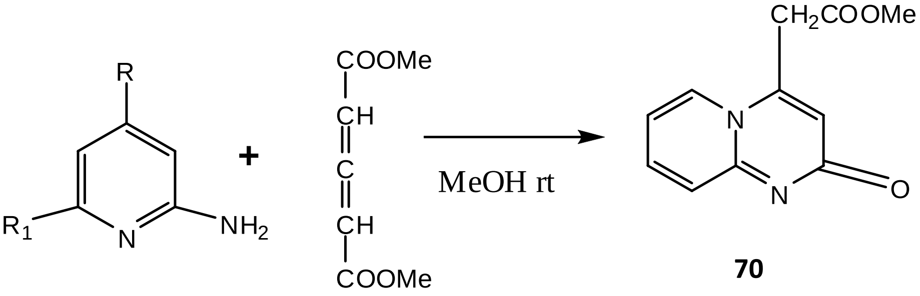
Cyclocondensation of 2-aminopyridines and ethyl cyno(hydroxyimino) acetate **67** in presence of NaOEt gave 4-amino-3-nitroso-4H-pyrido[1,2-a]pyrimidin-2-ones **68** **(Del Gandice et al, 1995).**



67

68

Methyl 2-oxo-2H-pyrido[1,2-a]pyrimidine-4-acetate **70** was prepared in the reaction of 2-aminopyridine and dimethyl penta-2,3-diendioate **69** under argon **(Gurinder et al, 1988).**

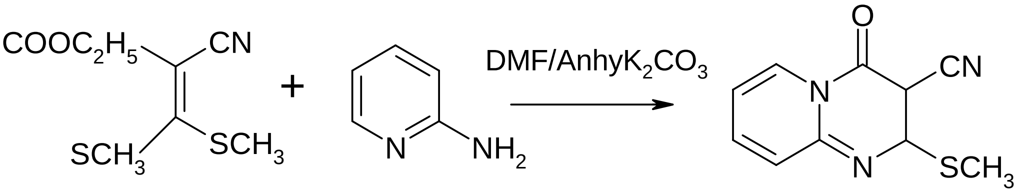


69

70

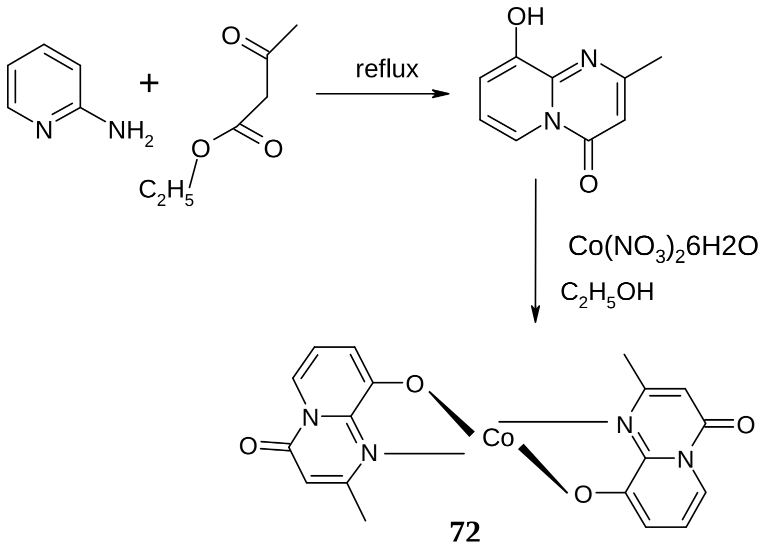
2.2 Synthesis of 4--oxo-4H-pyrido[1,2-a]pyrimidinone

The synthesis and antimicrobial activity of 3-cyano-2-(methylthio)-4-oxo-4H-pyrido[1,2-a]pyrimidine **71** and their derivatives were reported by **Sambhaji Vartale et al, 2011.**



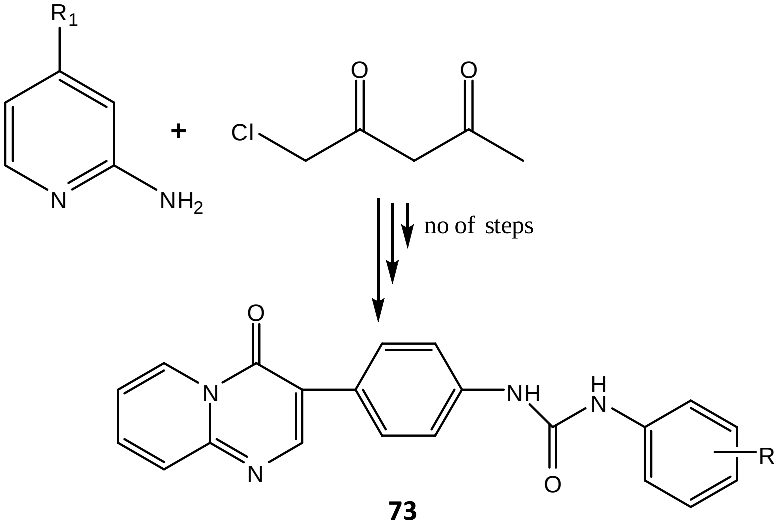
71

Cobalt (II) complexes of 2-methyl-4-oxo-pyrido[1,2-a]pyrimidine **72** were prepared and their spectroscopic and crystal structure were studied by **Huaihong Zhang et al, 2011.** The complex existed as a mononuclear complex with distorted square-pyramidal geometry.



72

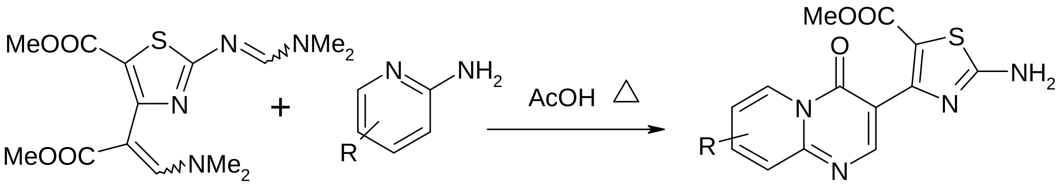
Diaryl urea derivatives **73** possessing a 4H-pyrido[1,2-a] pyrimidine-4-one group were found to be potent anticancer compounds **(Peng YaO et al, 2010).**



73

A blue-emitting organic, 9-hydroxyl–3– hydroxylethyl– 2 –methyl – 4H–pyrido[1,2-a)pyrimidin–4– one was synthesized by **Huaihong Zhang (2010)** from 2-amino-3-hydroxylpyridine and 2-acetylbutyrolactone**.** At room temperature, the compound exhibited an intense blue emission at 432 nm upon 323 nm excitation in the solid state. The thermal stability of the compound was also investigated by thermogravimetric analysis.

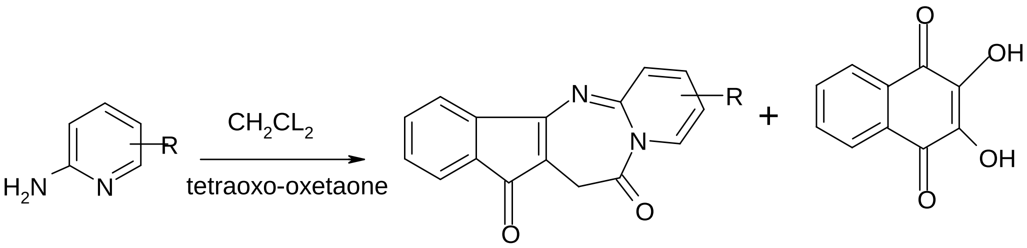
Methyl 2-amino-4-(2-methoxy-2-oxo-ethyl)thiazole-5-carboxylate prepared from dimethylacetone-1,3-dicarboxylate **74**, sulfuryl chloride and thiourea was transformed in two steps into (4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates **75 (Martina Žugelj et al, 2009).**



74

75

The reaction of 2-aminopyridines with tetra oxo-oxetanone in dichloromethane afforded the indeno[1,2,d] pyrido[1,2-a]pyrimidines **76** and dihydroxy quinine **77** in good yields. The synthesized compounds were found to be inhibitors of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor 2 (VEGFR-2) and Flt-4-Kinases. Hence indeno pyrido pyrimidine diones were regarded as valuable agents in the discovery of drugs for cancer treatment **(Maria Tsana Kopoulou et al, 2008).**

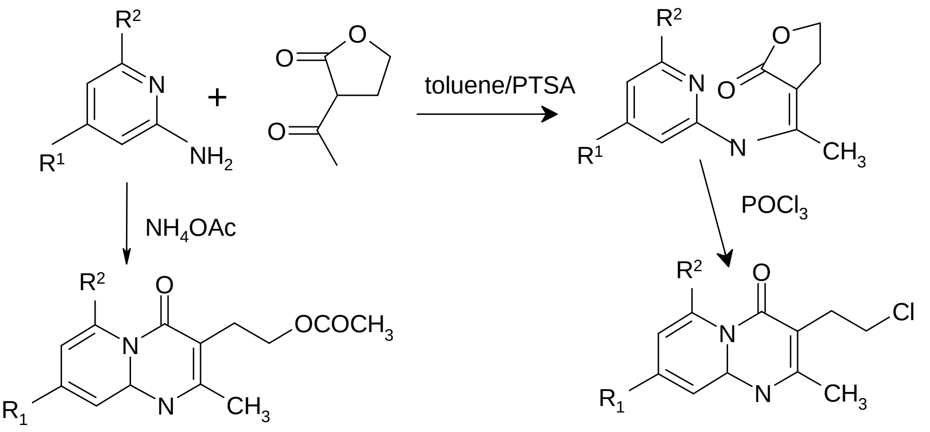


76

77

R = H; 8Methyl; 4Methyl; 6Methyl; 4, 6 dimethyl; 5Chloro; 3-hydroxy

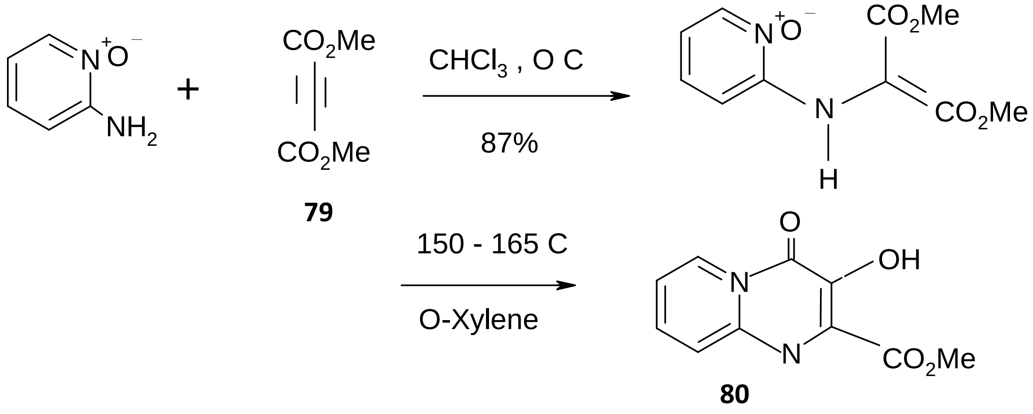
A new method was developed by **Raghunath Toche et al, 2008** towards the synthesis of pyrido [1,2-a] pyrimidines with 3-hydroxy and 3-chloro ethyl side chain. The reaction involved the condensation of 2-amino pyridines with acetyl butyrolactone intermediates which on cyclisation with phosphorous oxy chloride or ethanol in sodium ethoxide yielded pyrido [1,2-a] pyrimidines **78a and 78b** in good yields.



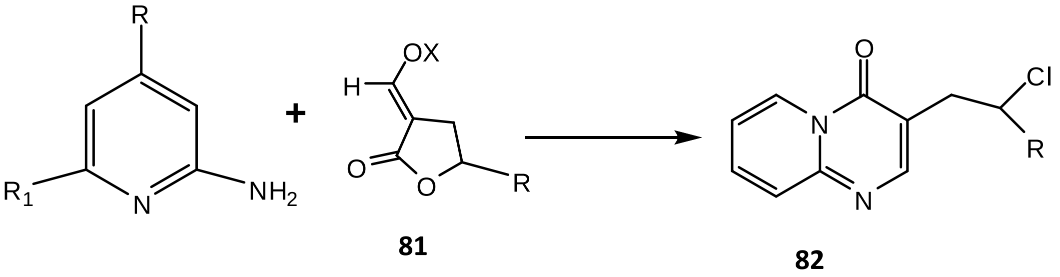
78a

78b

An efficient and reliable synthesis of the heterocyclic scaffold methyl–3–hydroxyl–4–oxo-4H-pyrido[1,2-a]pyrimidine–2–carboxylate **80** was described by **Olaf Kinzel et al, (2008),** from 2-aminopyridine N-oxide and dimethyl acetylene dicarboxylate **79** in chloroform at O°C.



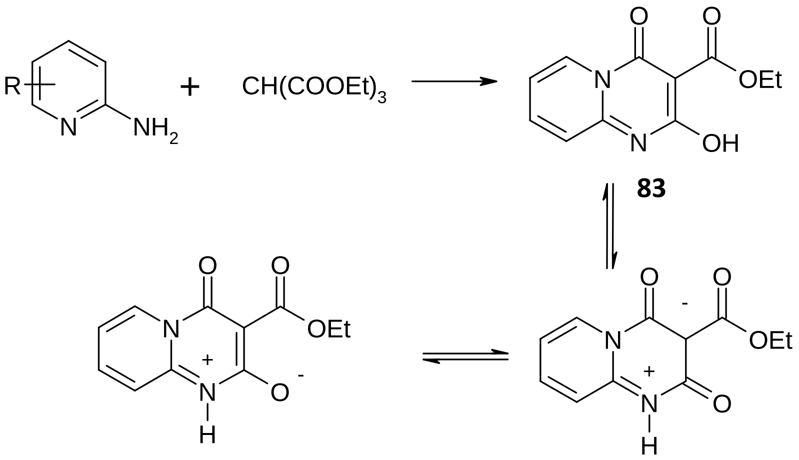
A highly efficient method was successfully developed for the synthesis of fused pyrimidines **82** via aminoheterocyclic dihydrofurnone intermediates from 2-aminopyridine and cyclic β-formylesters **81** by three different methods **(Raghunath Toche et al, 2007).**



R=H, CH_3 X=Na^+

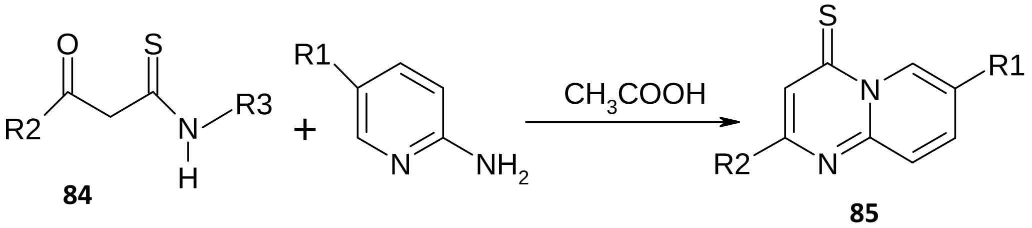
Method A= toluene/p-TsOH; Method B = $NH_4OAc/120^0C$; Method C= CH_2Cl_2/rt

An improved method for the preparation and purification of ethyl-2-hydroxyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylates **83** was proposed by **Ukrainets et al, 2007**. ^1H and ^{13}C NMR and X- ray analysis of the compounds showed that in DMSO solution it existed as 2-hydroxy-4oxo form while in the crystalline form it occurred in the bipolar 2,4-dioxo form.



83

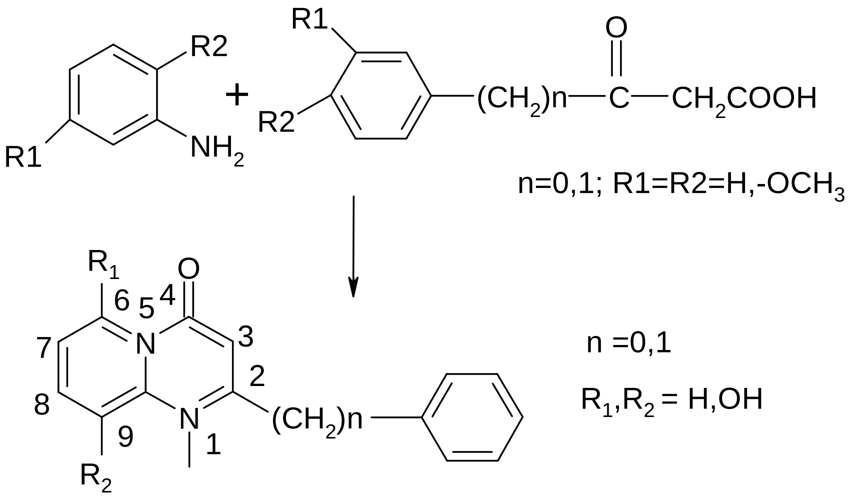
Britsun et al, 2007 reported the formation of 4H-pyrido[1,2-a]-pyrimidine-4-thiones **85** by the reaction between 3-oxo-propanethioamides with 2-amino -5-R-pyridines **84**.



84

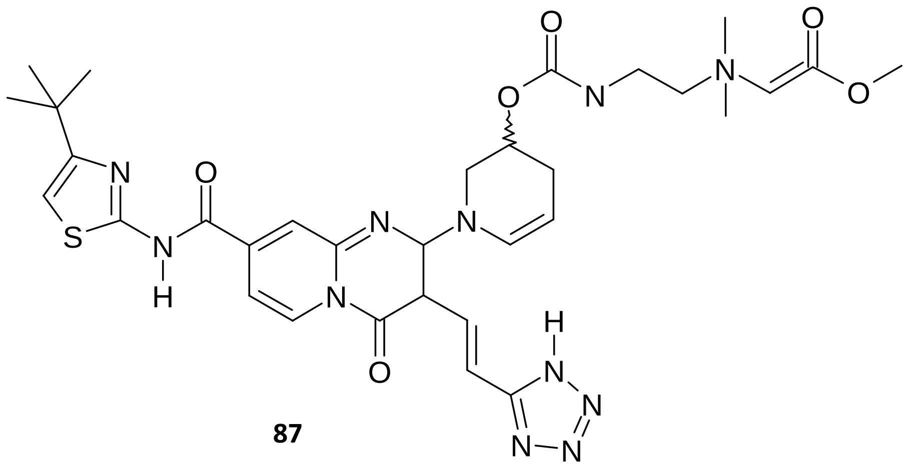
85

2-phenyl-pyrido[1,2-a] pyrimidin-4-one derivatives **86** bearing a phenol or a catechol moiety in position 2 were tested as aldose reductase (ALR2) inhibitors and exhibited activity levels in the micromolar / submicromolar range. Introduction of a hydroxyl group in position 9 gave an enhancement of the inhibitory potency. Lengthening of the side chain to benzyl determined a general reduction in activity. The lack or the methylation of the phenol or catechol hydroxyls gave inactive or scarcely active compounds, thus demonstrating that the phenol or catechol hydroxyls are involved in the enzyme pharmacophore recognition. All the pyrido pyrimidinones displayed significant antioxidant properties, with the best activity shown by catechol derivatives. The theoretical binding mode of the most active compounds obtained by docking simulations into the ALR2 crystal structure was fully consistent with the structure activity relationships in the pyrido [1,2-a] pyrimidin-4-one series **Concettina Motta et al, 2007.**



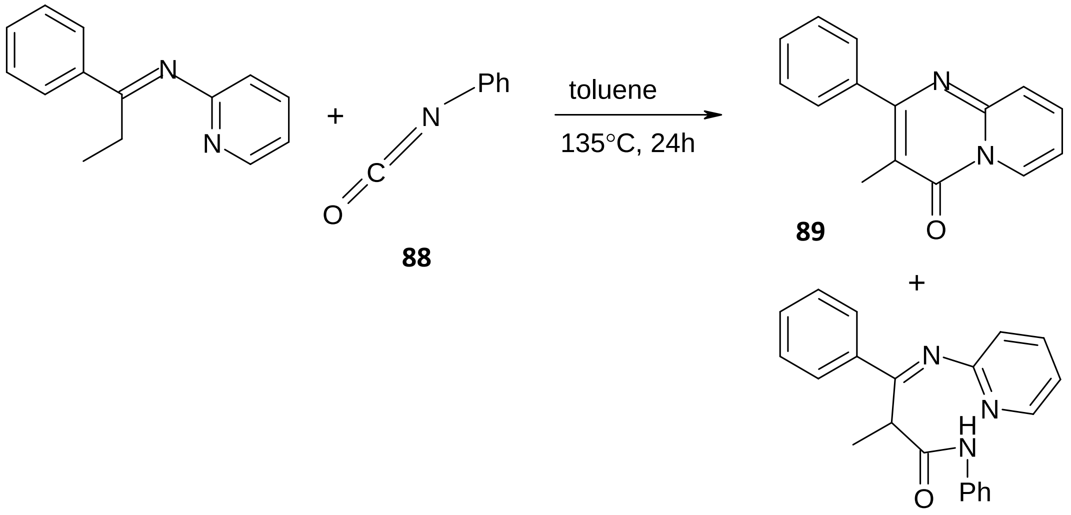
86

A series of 4-oxo-4H-pyrido[1,2-a]pyrimidine derivatives **87** substituted at the 2-position with piperidines bearing quaternary ammonium salt side chains, were synthesized and evaluated, for their ability to potentiate the activity of the fluoxoquinolone levofloxacin (LVFX) and the β - lactam aztreonam (AZT) in pseudomonas aeruginosa, by **Ken-ichi Yoshi da et al, 2007.**

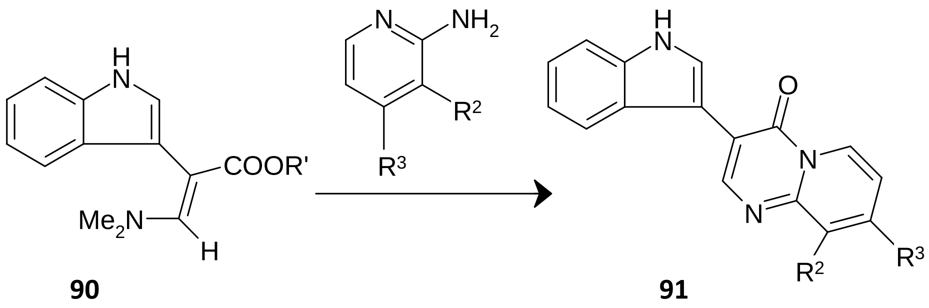


87

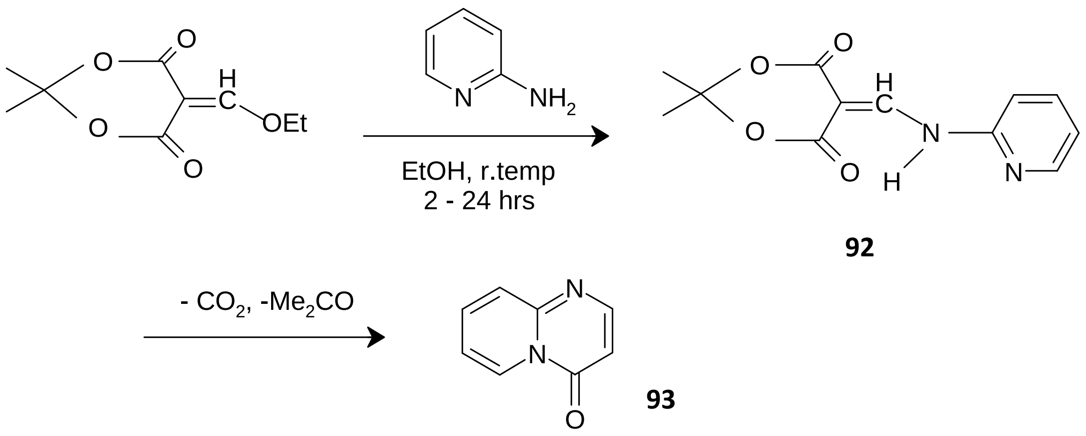
Yoichiro Kuniobu et al, (2006) prepared 4H pyrido [1, 2-a] pyrimidin-4-ones **89**, by the reaction of ketimines **88** bearing a pyridyl or a picolyl group on a nitrogen atom of the imine moiety with tosyl isocyanate in toluene at 135°C for 24h, in quantitative yields. In these reactions tosyl isocyanate acts as a carbonyl precursor and the pyridyl or picolyl group is a key functional group.



Methyl and ethyl 3-dimethyl amino-2 (indol-3-yl) propenoate were prepared from alkyl 3-indole acetates and ter butoxyl bisdimethyl amino) methane and treatment of thise N, N-dimethyl enaminone **90** with 2-aminopyridines as N, N, 1-2 dinucleophiles, yielded 3-(1H-indol-3yl) – 8 methyl–4H pyrido[1,2-a] pyrimidin–4 ones **91** in moderate yields **Renata Jakse et al, (2004).**



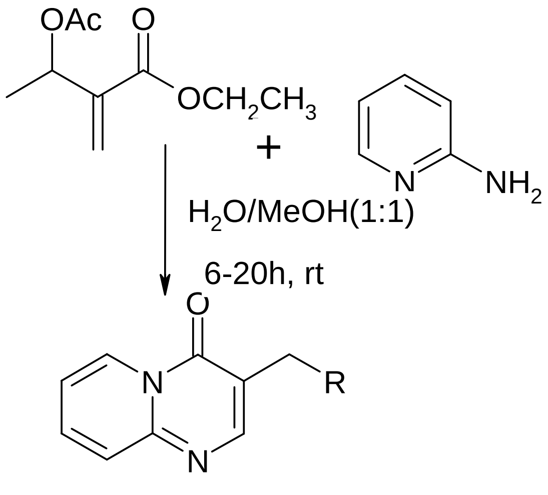
Ravina et al, (2002) obtained 4-oxo-4H-pyrido[1,2-a]pyrimidines **93** by melting 2-pyridylamino methylene iso propylidene malonates **92**. 2-pyridylamino methylene iso propylidene malonates were prepared from ethoxymethylene isopropylidene malonates and 2-amino pyridines in ethanol at room temperature for 2-24h. When the pyridyl amino methylene malonates were heated to their melting points, the dioxane ring opened with evolution of acetone, which was followed by decarboxylation and cyclisation to afford the 4-oxo-4H-pyrido [1,-2-a] pyrimidines.



92

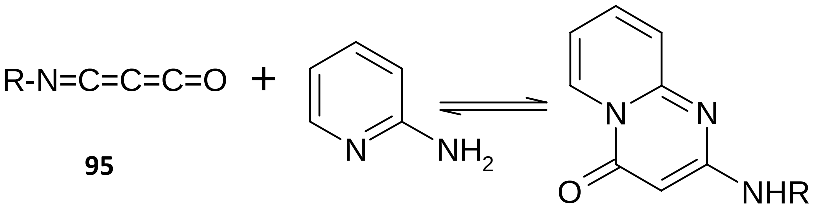
93

A facile one-pot convenient transformation of the acetates of Baylis-Hillman adducts into fused pyrimidones i.e 3-substituted-1,5-diazabicyclo(4.4.0) deca-2,5,7,9-tetraen-4-ones **94** via reaction of 2-aminopyridine in environmentally friendly aqueous media was described by **Deevi Basavaiah et al, 2002**.



94

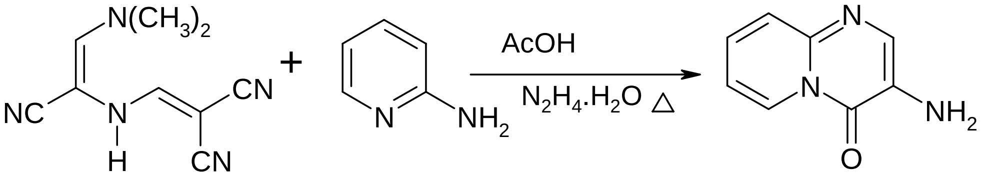
The nucleophilic addition of primary 2-amino pyridines with stable (neopentylimino)-, (mesitylimino)- , and (o-tert-butylphenylimino) propadienones **95** were investigated by **Herve Bibas et al, (2002).** The reaction was initiated by the nucleophilic attack of the amine on the cumulenic carbonyl group to generate zwitterion intermediates which tautomerize to mesoions Subsequent ring closure reaction produced pyridopyrimidinones **96** as major or exclusive product in methylene chloride at room temperature.



95

96

The applicability and synthetic potency of the new reagent *N*-(2,2-dicyanoethenyl) aminoacetonitrile **97** to develop an expeditious convenient synthetic route to unique poly functionally substituted pyrroles, heterocyclo pyrimidines **98** and 2*H*-1-benzopyran-2-ones were reported with chemical and spectroscopic evidence for the structures of the newly synthesized compounds **(Ayman Erian et al, 2001).**

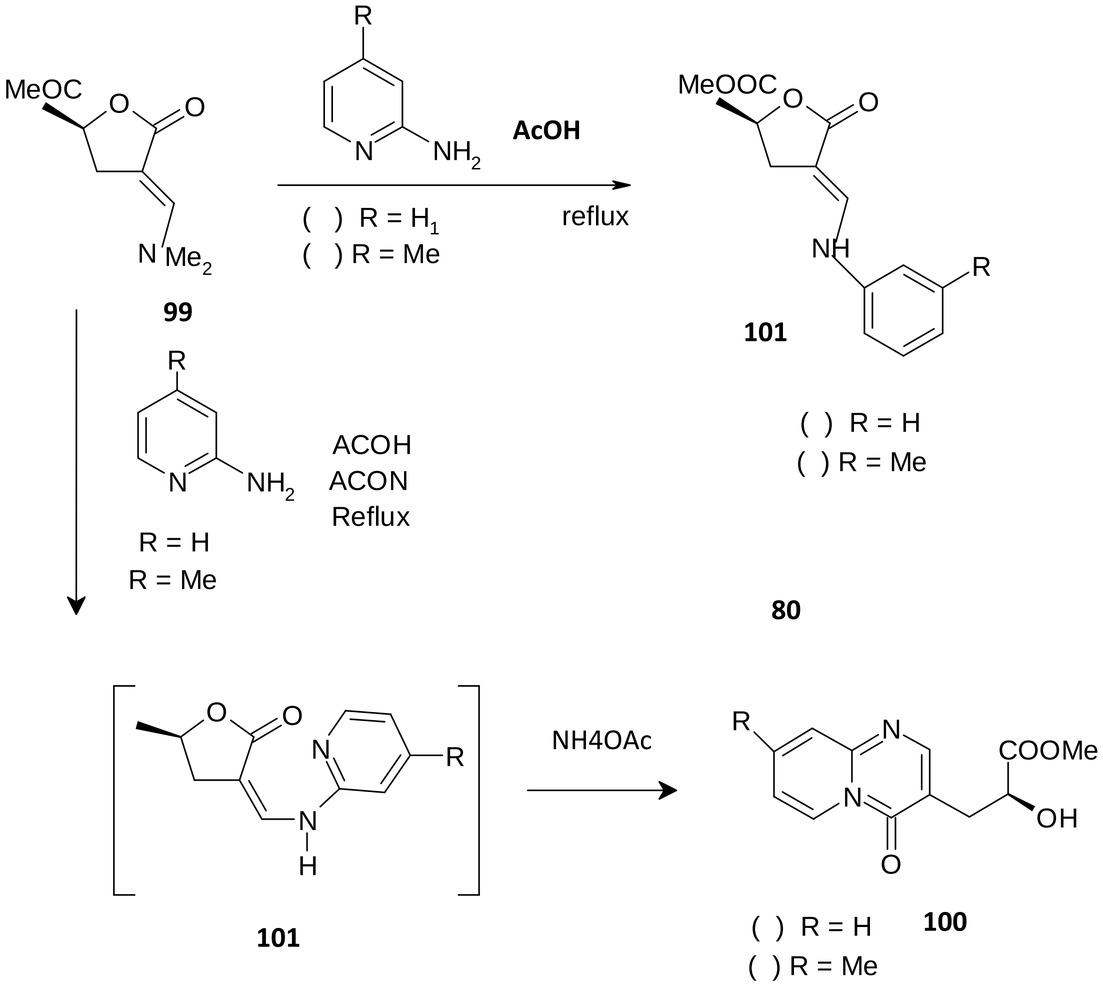


97

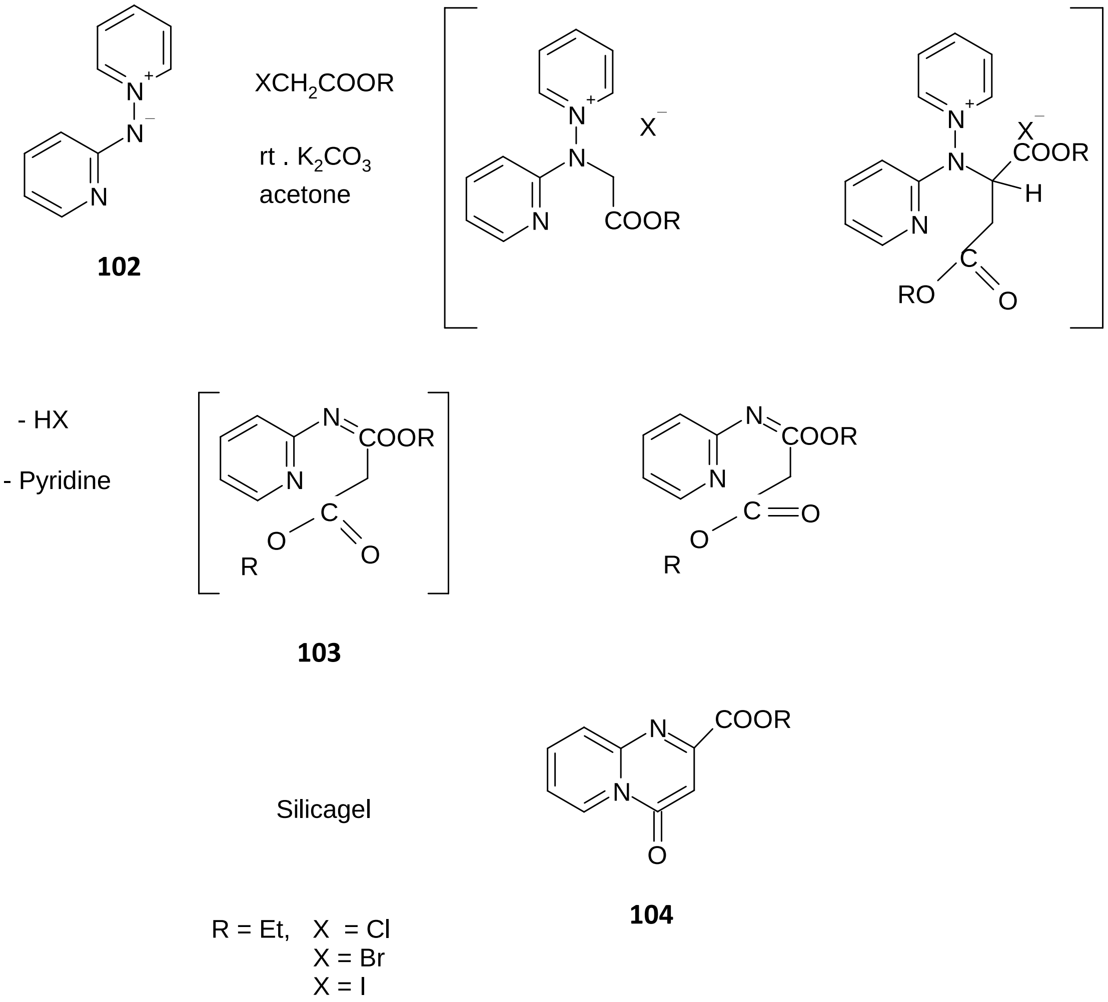
98

A one step ‘ring switching’ transformation of (s)-3-[(dimethylamino)methylidene] -5- (methoxycarbonyl) tetra hydrofuran-12-one **99** with 2-amino pyridines afforded 3-(4-oxo-4H pyridine [1,2-a] pyrimidinyl-3) -2-hyroxy propanoates **100.** The reaction of **99** with 2-amino pyridine or 2-amino-4-methylpyridine in refluxing acetic acid gave only the substitution product **101**. The presence of sodium acetate was required to achieve the transformation of **101** into the corresponding methyl-3-(4-oxo-4H-pyrido[1,2-a]pyrimidinyl-3)-2-hydroxy propanoate **100 (Markoskof et al, 2000).**

R = neopentyl; mesityl; o-tert-butylphenyl



Reaction of pyridinium-N-(2-pyridyl) amidine **102** and alkyl haloacetates in the presence of potassium carbonate afforded a mixture of 4-oxo-4H-pyrido[1,2-a] pyrimidine–2-carboxylates **104** and 2-aminopyridine derivatives through intermediates. Compound **103** could be cyclised by the action of heat or silica gel into **104.** The best yield was achieved in the case of ethyl bromoacetate **(Dela Rosa et al, 2000).**



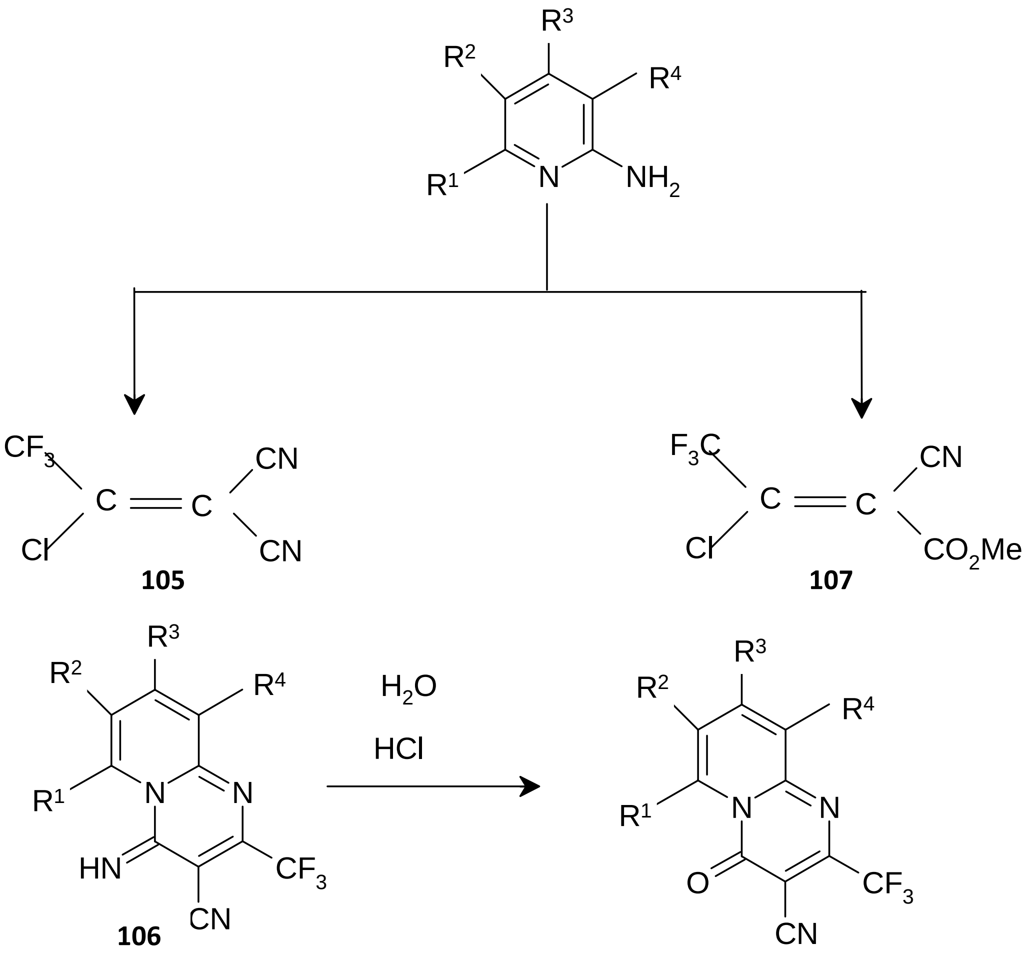
102

103

104

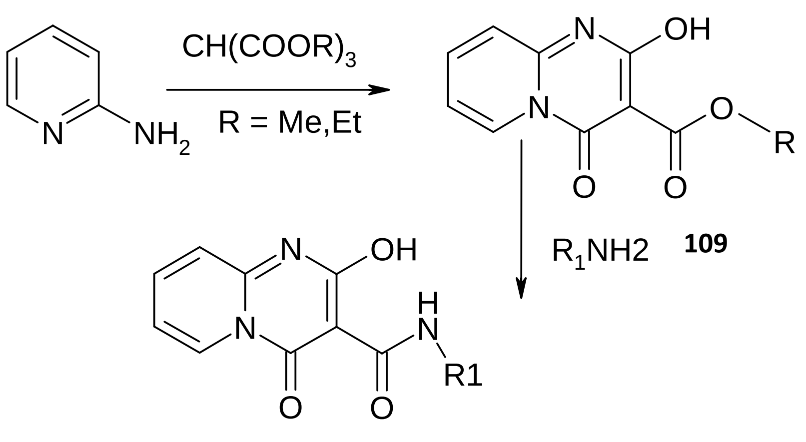
R = Et, X = Cl
X = Br
X = I

The reactions of 2-aminopyridine with 2-chloro–1,1 dicyano–2– trifluoro methylethylene **105** in chloroform at room temperature afforded, 3 cyano-4-imino-2– trifluoromethyl-4H-pyrido[1,-2-a]pyrimidines **106** in 51-84% yields. Under analogous conditions, 2-amino pyridine with 2-chloro-1-cyano-1-methoxycarbonyl-2-trifluoromethyl ethylene **107** afforded, 3-cyano-2-trifluoromethyl–4H–pyrido[1,2-a]pyrimidin–4–ones **108** in 23 – 53% yields. The NMR and X-ray diffraction analysis showed that the first stage of the reaction involved the alkenylation of the exocyclic nitrogen atom of 2-aminopyridine followed by the formation of pyrido[1, 2-a] pyrimidines **(Shidlovski et al, 2000).**



105 107 106 108

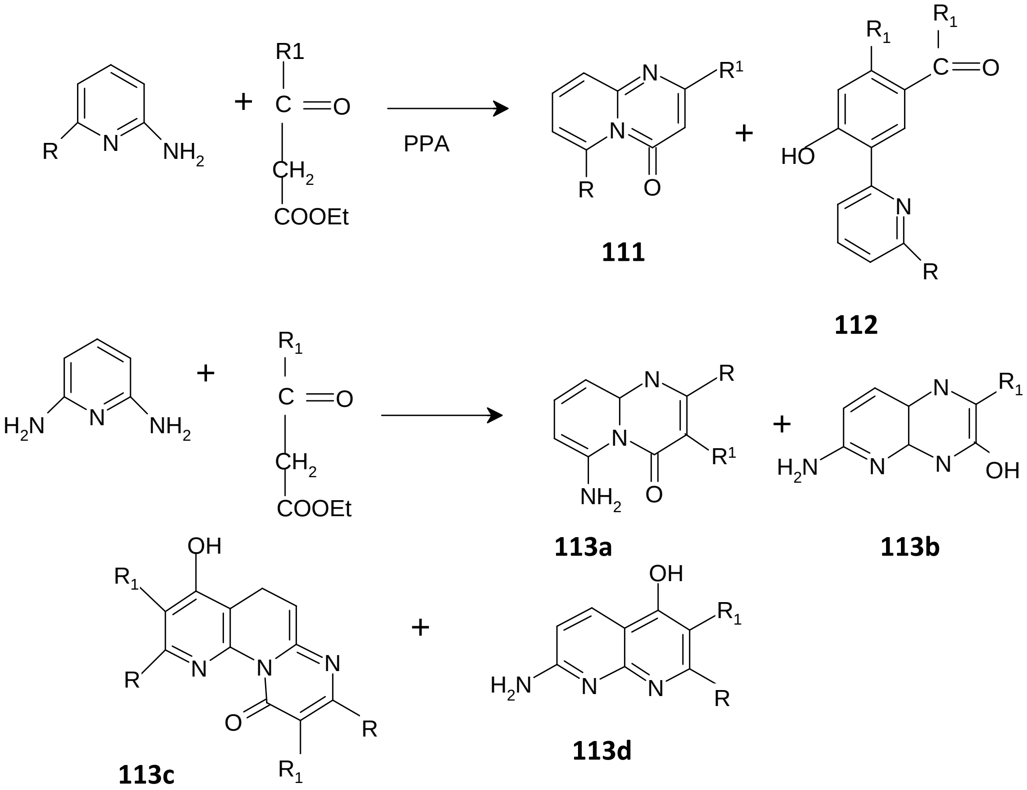
The reaction of methane tricarboxylates with 2-aminopyridine, yielded heteroaryl carboxylic acid esters **109** These heterocyclic esters were used to obtain a number of heteroaryl carboxylic amides **110** bearing various substitutes on the carboxamide group **(Alexander Kutyrev et al, 1999).**



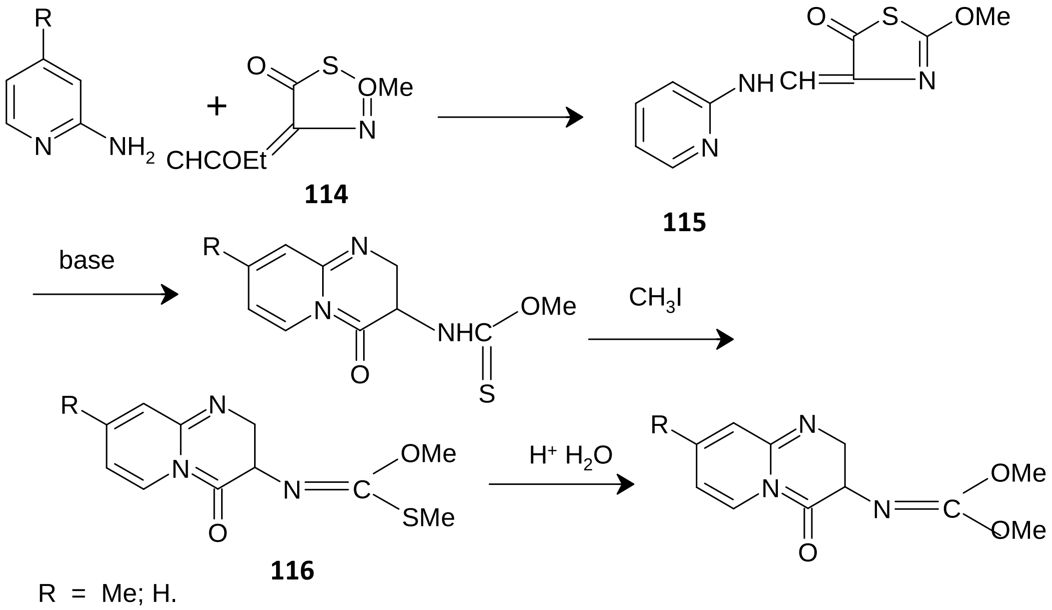
109

110

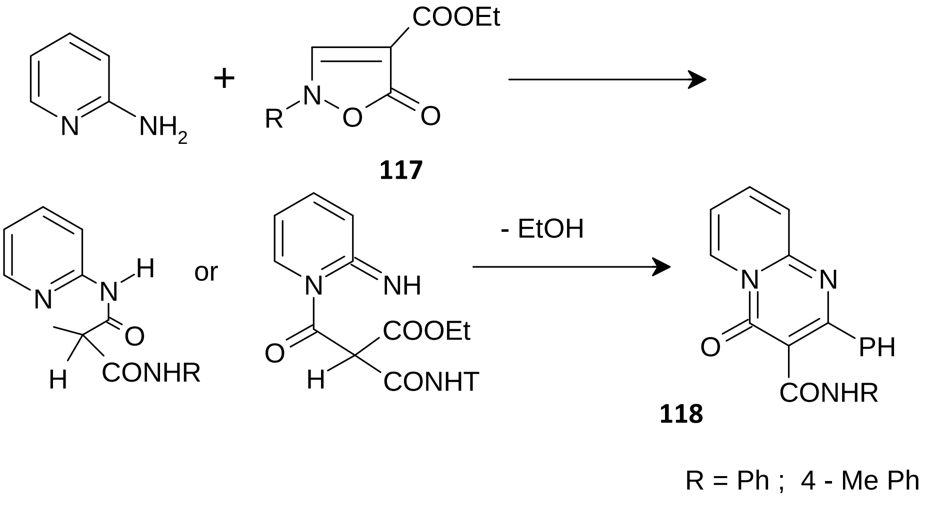
Pier Luigi Ferrarini et al, (1999) reported the synthesis of 4H-pyrido [1, 2-a] pyrimidin–4-ones **111** along with pyridine-2-ones **112** by the condensation of 2-aminopyridine with ketocarboxylic esters in polyphosphoric acid at 100^0 C. In the case of condensation of 2,6-diamino and 2-acetamido-6-aminopyridine with ketocarboxylic acid esters, a mixture of products **113a, 113b, 113c, 113d** were obtained.



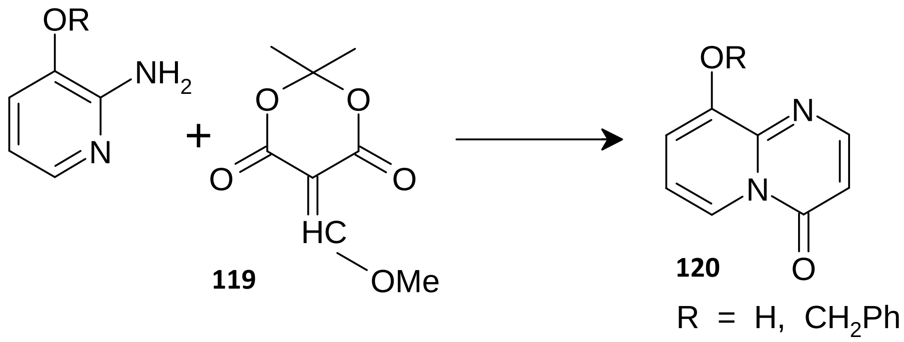
The reaction of 2-amino pyridine derivatives with 2–methyoxy–4–ethoxymethylene–5(4H)–thiazolone **114** afforded 4-heteroaryl aminomethylene–2 methoxy – 5(4H) – thiazolones **115**. They were transformed into the corresponding pyrido[1,2–a] pyrimidines **116** in presence of a base or a nucleophile **(Janez Smodis et al, 1994).**



Ricardo Bossio 1993, reported the reaction between 2-substituted ethyl 2,5-dihydro–5–oxoisoxazole–4–carboxylates **117** and 2-aminopyridine. The reactions were performed by heating the two reactants in the absence of a solvent to give the product, N– substituted–2-hydrooxy-4-oxo-4H-pyrido[1,2-a]pyrimidine–3–carboxamide **118**.



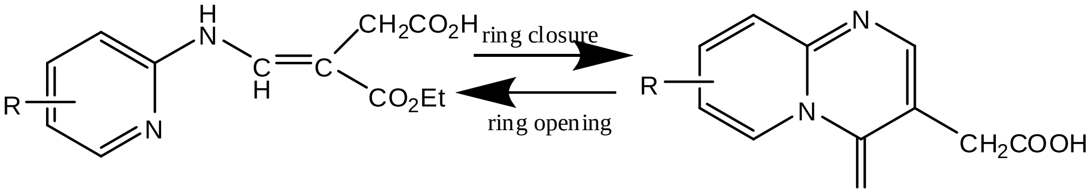
9 – hydroxyl-pyrido[1,2-a]pyrimidin–4–one **120** was prepared by condensation of 2-amino–3–hydroxyl-pyridine with isopropylidene amino methylene malonate **119**. The reaction first led to an enamino ester intermediate which underwent cyclization by heating at 250°C, to afford 9-hydroxy pyrido [1,2-a]pyrimidin–4–one **(Dennin et al, 1991).**



119 **120**

$R = H, CH_2Ph$

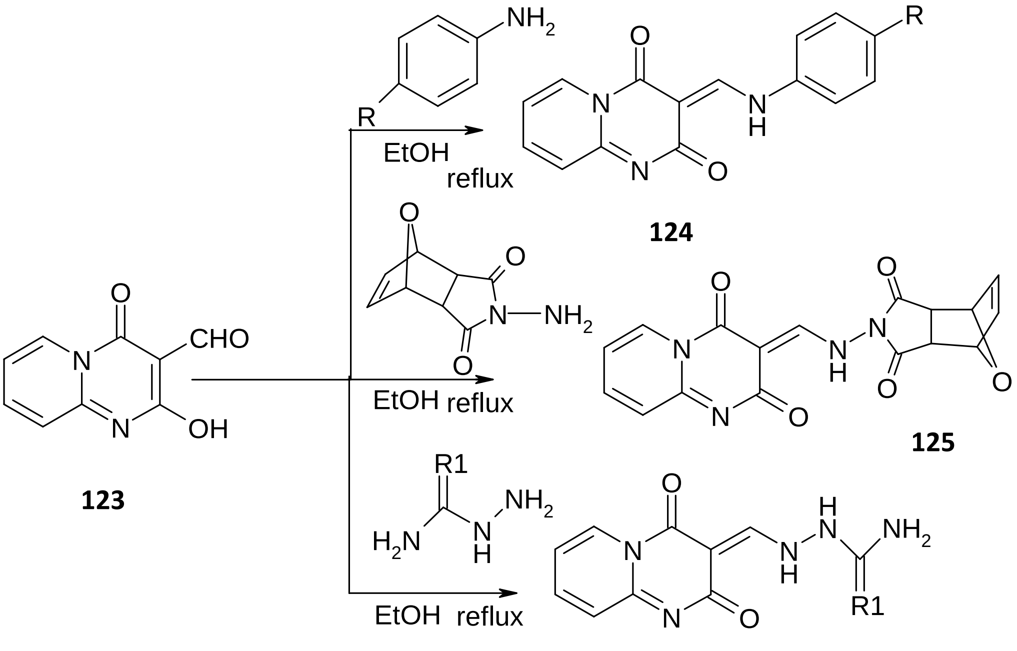
A method to synthesize pyridopyrimidine acetic acid include reversible ring closure of 2-(2-Pyridylaminomethylene) succinates, in ethanolic sodium ethoxide solution with lower yields (35%) **(Lelle Vasvari-Debreczy et al, 1988).**



121 **122**

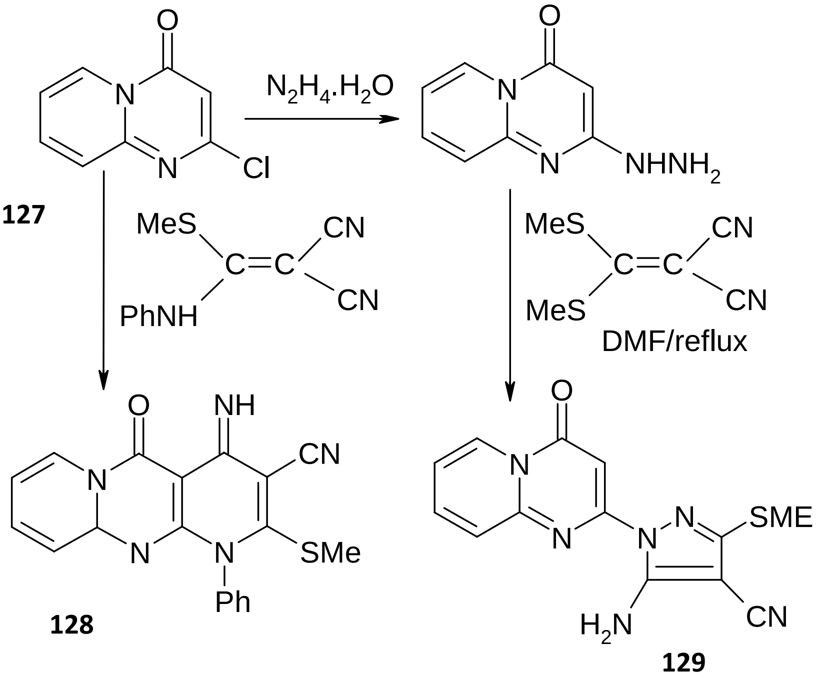
2.3. Reactions of 4-oxo-4H-pyrido[1,2-a]pyrimidinones

Reactivity of 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbaldehyde **123** towards N- and C- nucleophiles was described by **Mohamed Abass et al, 2010a.** A series of new enaminones **124**, Schiff's base **125** and hydrazinomethylene diketones **126** were prepared in good yields.

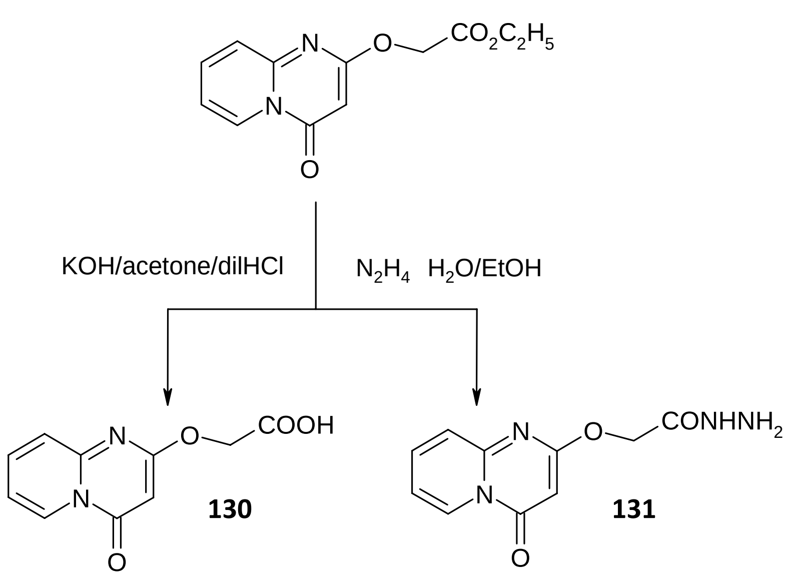


123 **124** **125** **126**

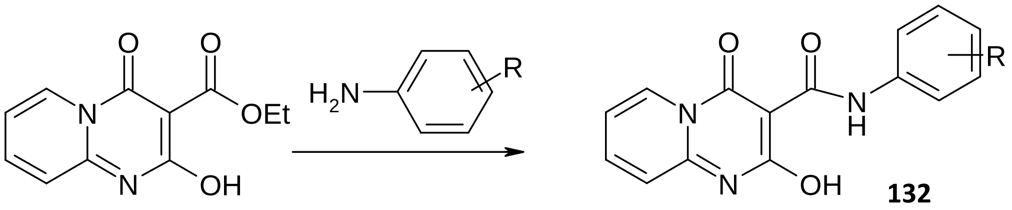
2-chloro-4H-pyrido[1,2-a]pyrimidin-4-one **127** was utilized as a synthone precursor to prepare novel heterocyclic systems **128** and **129** by **Mohamed Abass et al, 2010b.**



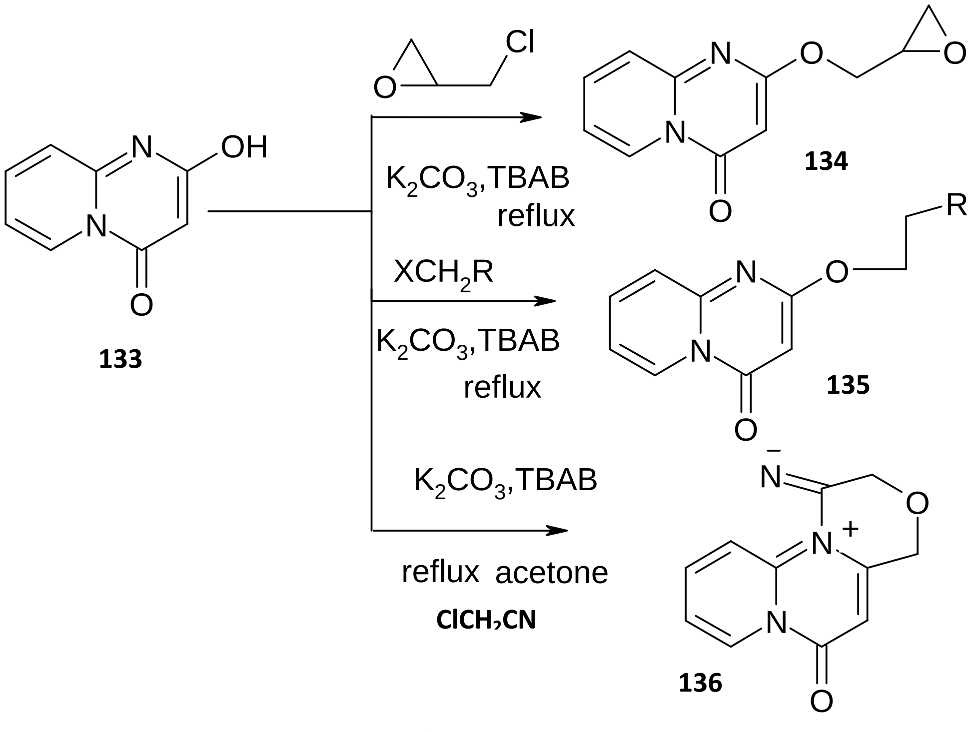
A series of novel bis-heterocyclic ethers, containing 4H-pyrido[1,2-*a*]pyrimidin-4-one along with other five and six-membered heterocyclic rings, was obtained utilizing ethyl [(4-oxo-4H-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetate,[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetic acid **130** and/or [(4-oxo-4H-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetohydrazide **131**. Some pyrazole, triazole, and oxadiazoline derivatives was also prepared from hydrazides **(Mohamed Abass et al, 2009).**



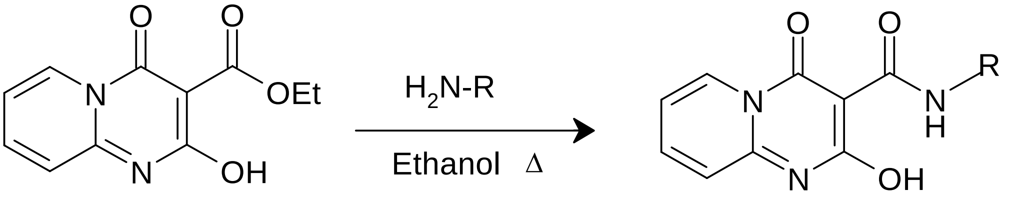
Alkyl, arylalkyl and aryl amides of 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid **132** were prepared and their diuretic properties were studied. The compounds significantly increased the diuretic kidney function **(Ukrainets et al, 2008).**



Alkylation of 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one **133** was investigated under solid– liquid phase transfer catalysis conditions (PTC), using tetrabutyl ammonium bromide and potassium carbonate. The reaction with alkyl halides led to the formation of various 2-alkoxy products **135**, in fair yields. Reaction of compound with epichlorohydrin and chloroacetonitrile, under the same PTC conditions, afforded novel -disubstituted glycerol **134** and oxazolo pyrido pyrimidone betaine **136** derivatives, respectively **(Mohamed Abass et al, 2007).**

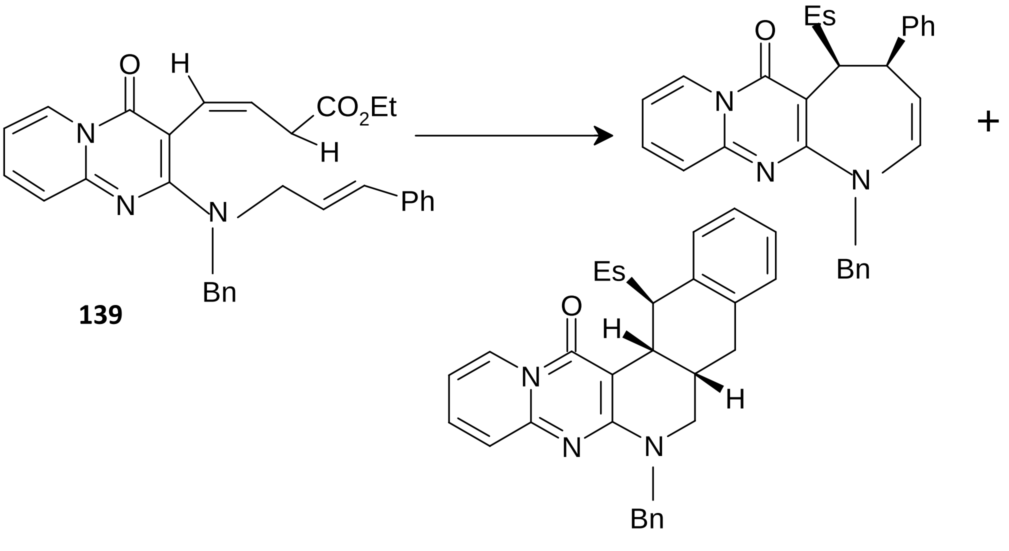


Dialkylamino alkyl amides of 2-hydroxy-4-oxo-4H pyrido [1,2-a] pyrimidine carboxylic acids **137** were obtained by the amidation of the ethylesters with an excess of alkylamino alkylamine in boiling ethanol. The structures of the synthesized compounds were confirmed by ^{1}HNMR spectra and also by X-ray studies. The X-ray structural analysis of the compounds revealed the presence of two strong intramolecular hydrogen bonds. The formation of the hydrogen bonds leads to significant redistribution of electron density in the pyrimidone fragment. These scaffolds were also found to be potential antiviral agents **(Ukrainets et al, 2007).**



138

Michiniko Noguchi et al, (2007) studied the thermal reaction of 2-N-alk-2-enyl-benzylamino-3-(2-substituted and 2,2-disubstituted) vinyl pyrido [1,2-a]pyrimidin-4(4H)-ones **139.** The reaction afforded the desired product along with the hetero Diels-Alder adducts. The Diel –Alder adduct was formed by the [4 + 2] cyclo addition reaction of the α, β unsaturated ester carbonyl moiety of the substituted vinyl as a diene and the alkenyl moiety as a dienophile.

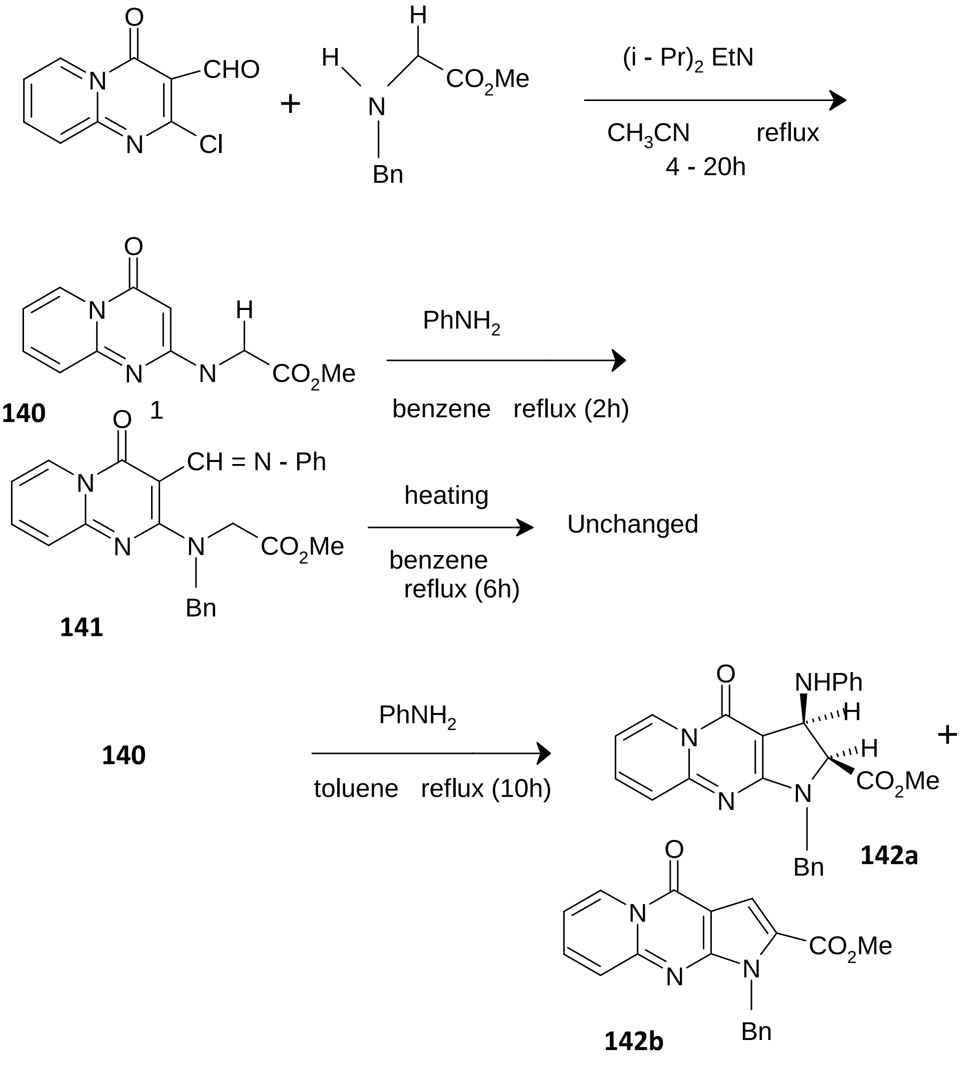


139

Michihiko Nogochi et al, (2003) studied the thermal reaction of N-benzyl-N(3-N-substituted imino methyl - 4-oxo- 4H pyrido [1,2a] pyrimidin-2- yl) amino acid esters **140**. The amino acid esters were obtained from aldehyde esters and primary amines. The thermal reaction of **140** with aniline in refluxing benzene gave the corresponding imine **141** but further heating did not give any change.

Similar reaction in refluxing toluene for 10 hours gave pyrroline derivative **142a** and full-conjugated pyrido pyrrolo pyrimidine **142b** with 28 to 38% yields respectively.

With t-butylamine the amino acid ester **140** in benzene at 50°C for 84h gave pyrroline derivatives **143** and **144** in 41 and 13% yields respectively. He also found that the reaction was stereo selective in yielding 2,3-dihydropyrido[1,2-a] pyrrolo [2, 3-d]pyrimidin-4(1H)-one.



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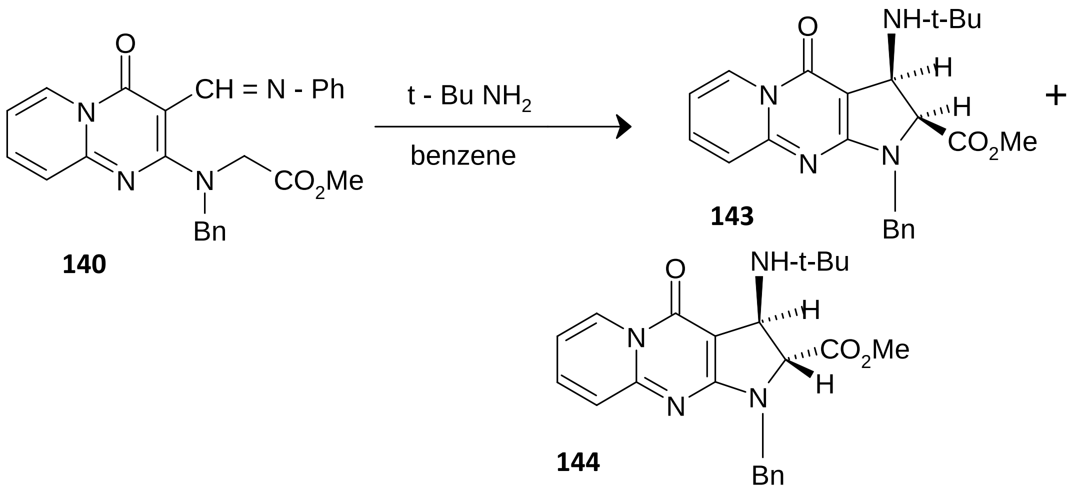
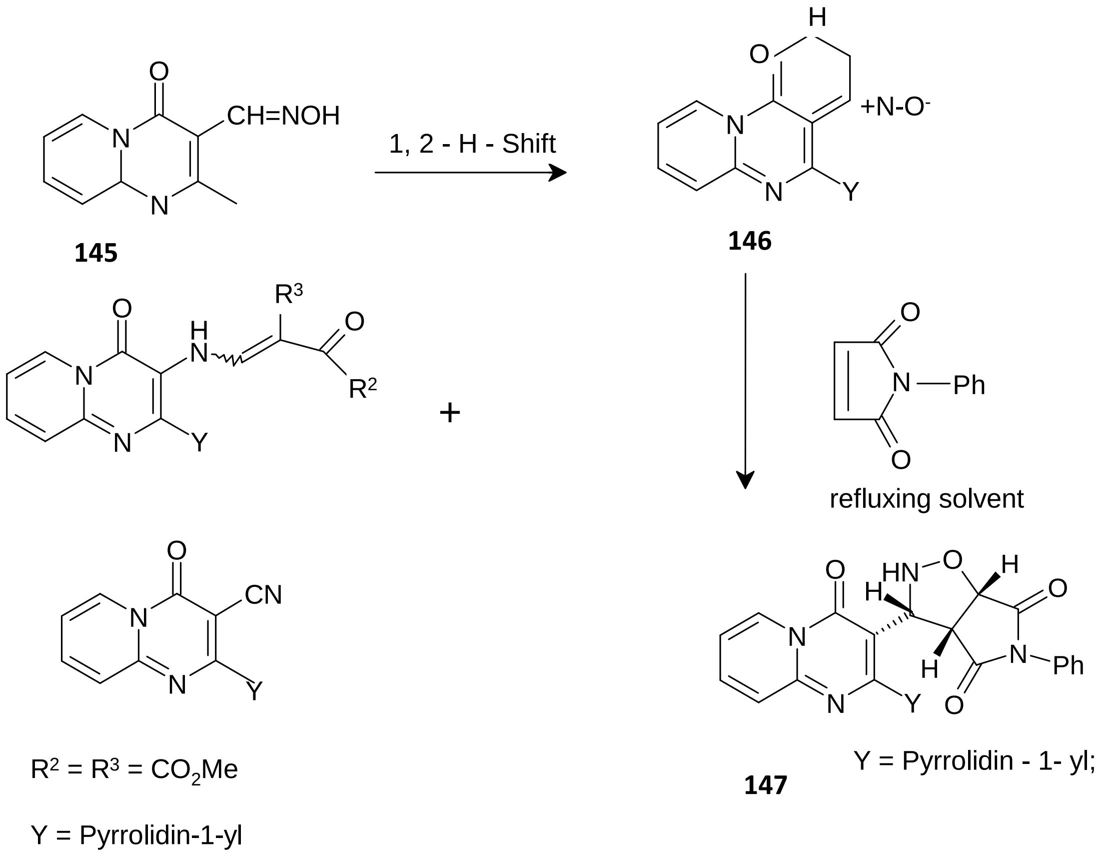
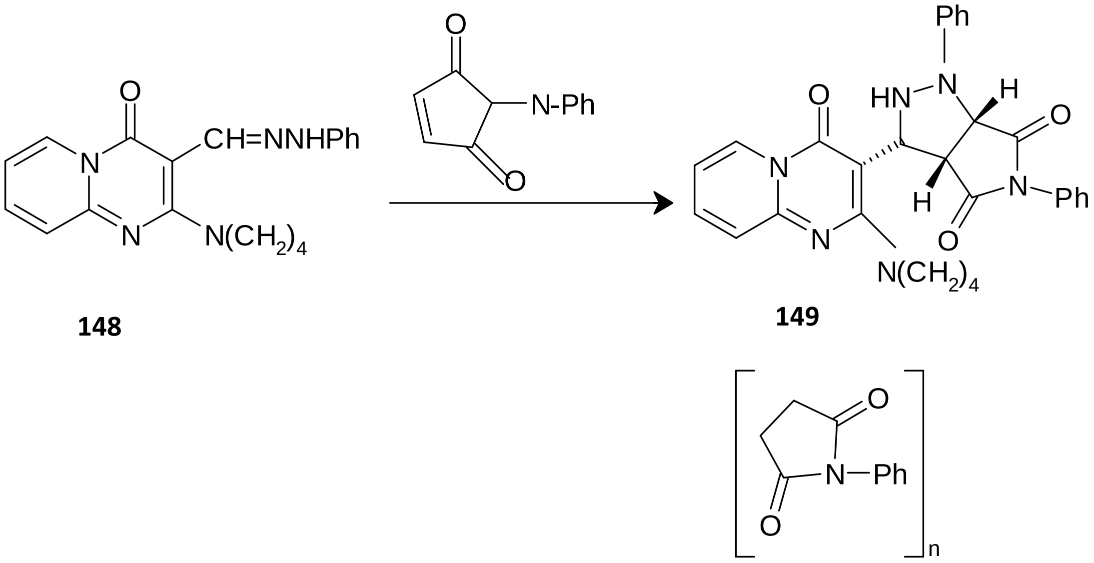


The oxime nitrone isomerisation through 1,2 hydrogen shift in 4-oxo-4H-pyrido[1,2-a]pyrimidine carbaldehyde **145** system was examined and their thermal behaviour in the presence of dipolarophiles was also studied. The reaction of oxime **146** with N-Phenyl maleimide (NPMI) in refluxing benzene for 36h gave isoxazolidine derivative **147** in 82% yield, as a single product **(Masashi Shirai et al, 2003).**



Similar reactions of the oxime **145** with other olefinic dipolarophiles such as dimethyl fumarate, dimethyl meleate and ethyl acrylate were unsuccessful. But the reactions at elevated temperature (i.e) in toluene under reflux gave mixture of many products, due to the decomposition of oxime **145**.

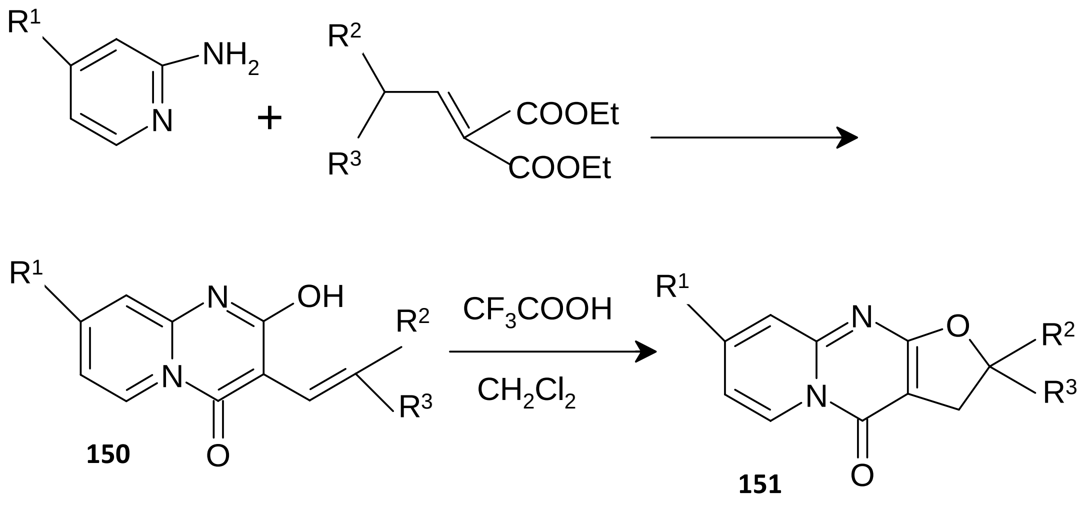
The thermal 1,2 hydrogen shift of 2-substituted 4-oxo-4H-pyrido[1, 2-a] pyrimidine–3-carbaldehyde phenyl hydrazones **148** were examined by **Michihiko Noguchi et al, (2003).** The NH-azomethine imines generated from the thermal 1,2 hydrogen shift of hydrazones underwent intermolecular cyclo addition reaction with olefinic electron-deficient dipolarophiles in a steroselective manner to yield pyrazolidine **149** derivatives.



148

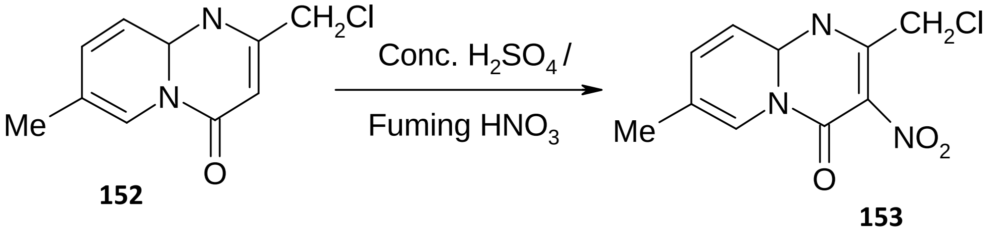
149

Cyclization of 3-alkenylpyrido[1,2-a]pyrimidines **150** in presence of acid catalyst under mild conditions afforded novel tricyclic furo[2,3-d]pyrido[1,2-a]pyrimidines **151** in high yields. The yield of the product was affected by the type and strength of the acid used. Exceptionally high yields were obtained when an organic acid like trifluoro methane sulfonic acid and trifluoro acetic acid were used. On the other hand, sulfuric acid gave the best results of the inorganic acids examined **(Gullu et al, 2003).**

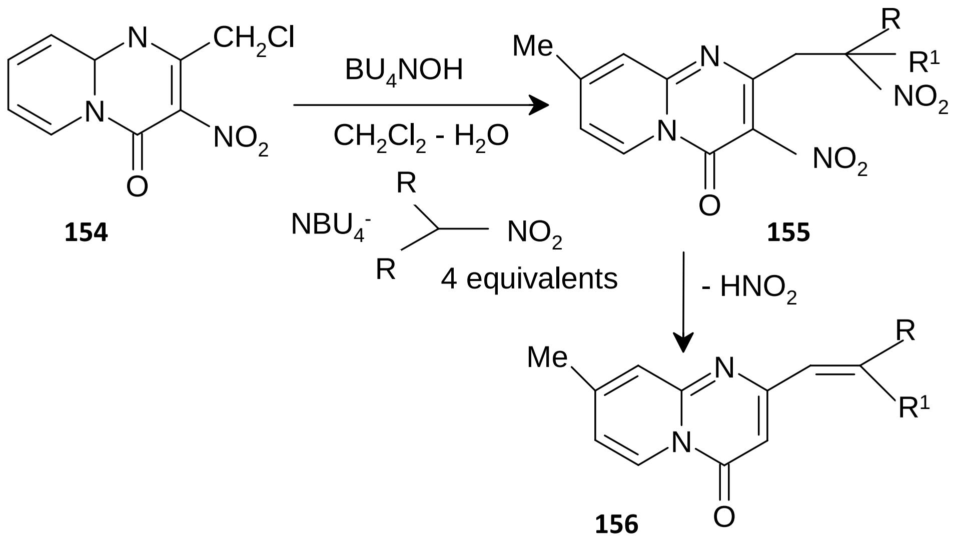


$R_1 = CH_3$; $R_2 = Ph$; $R_3 = CH_3$; $R_1=R_2=R_3 = CH_3$

Nitration of 2-chloromethyl–7–methyl–4H–pyrido[1,2-a]pyrimidin– 4–one **152** in concentrated H_2SO_4 with fuming HNO_3 at O°C yielded the 3-nitroderivative **153 (Djekov et al, 2001).**

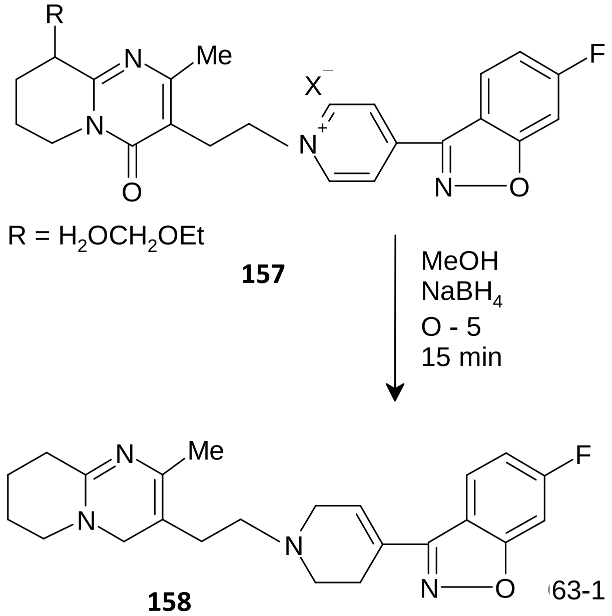


The same authors reported the reaction of 2–chloromethyl–4H-pyrido[1,2-a]pyrimidin–4–one **154** with various nitronate anions. Under phase – transfer conditions with BU_4NOH in water and dichloromethane under photo-stimulation pyrimidine-4-one gave 2-ethylenic derivatives **156.** When the ethylenic derivative was unsymmetrical only the E isomer was isolated. The product was formed by single electron transfer, C-alkylation and base promoted HNO_2 elimination from **155.**



154 **155** **156**

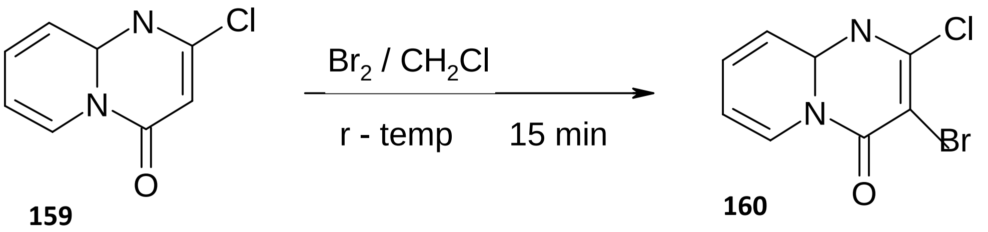
Reduction of Pyridinium salts **157** with NaBH$_4$ gave 3–[2[4–(6–fluoro –1,2–benzisoxazol–3yl)–1,2,3,6–tetrahydro–1–pyridyl]–ethyl]–2– methyl–6,7,8,9–tetrahydro–4H–pyrido[1,2-a]pyrimidin–4– ones **158 (Huguet et al, 2000).**



157

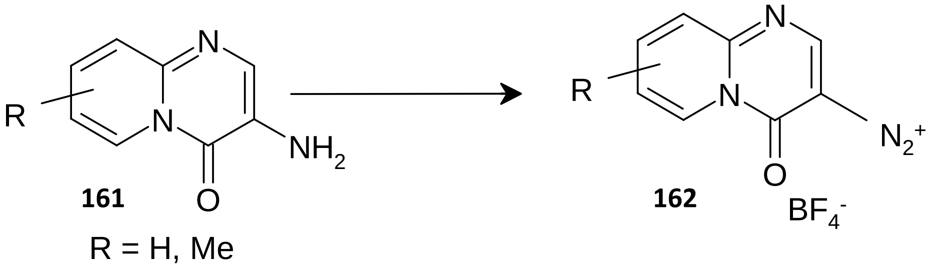
158

Bromination of 2-chloro–4H–pyrido[1,2-a]pyrimidone **159** with bromine in a mixture of dichloromethane and pyridine at room temperature for 15 minutes gave a 3-bromoderivative **160.** Nitration of 2-(1-piperazinyl)-4H-pyrido[1,2-a]pyrimidin-4-one with 99% HNO$_3$ in 96% H$_2$SO$_4$ at O°C gave 3-nitro derivative **(Roma et al, 2000).**



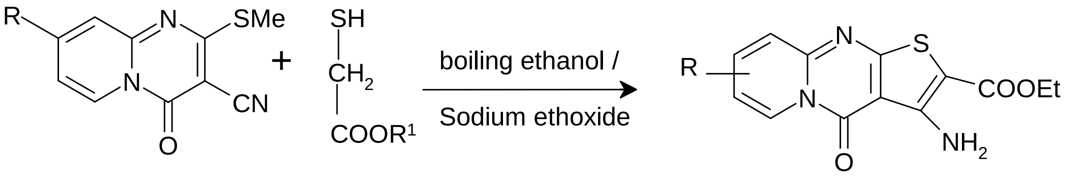
159 **160**

3-amino–4H–pyrido[1,2–a]pyrimidin–4–ones **161** were transformed into the stable 3-diazonium tetrafluoroborates **162** by treatment with $NaNO_2$ in 1:1 HCl below O°C, then with 50% HBF_4 or with t-$BUNO_2$ and BF_3:EtO_2 in CH_2Cl_2 at - 15°C **(Reanik et al, 2000).**



161 **162**

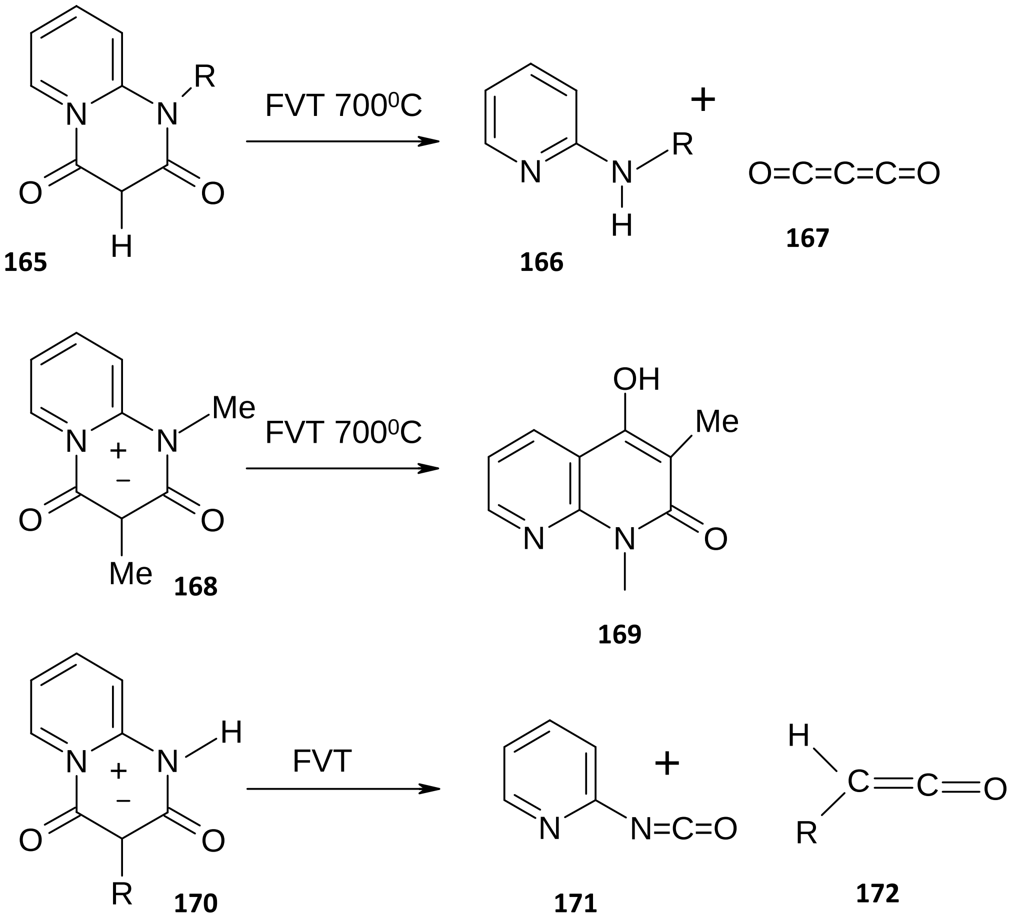
Cyclo condensation of 3-cyano-2-methyl thio-4H–pyrido[1,2-a]pyrimidin-4-ones **163** and ethyl mercaptoacetate in boiling ethanol in the presence of sodium ethoxide afforded 4H-pyrido[1,2-a]thieno[2,3-d] pyrimidin–4 ones **164 (Charris et al, 2000)**



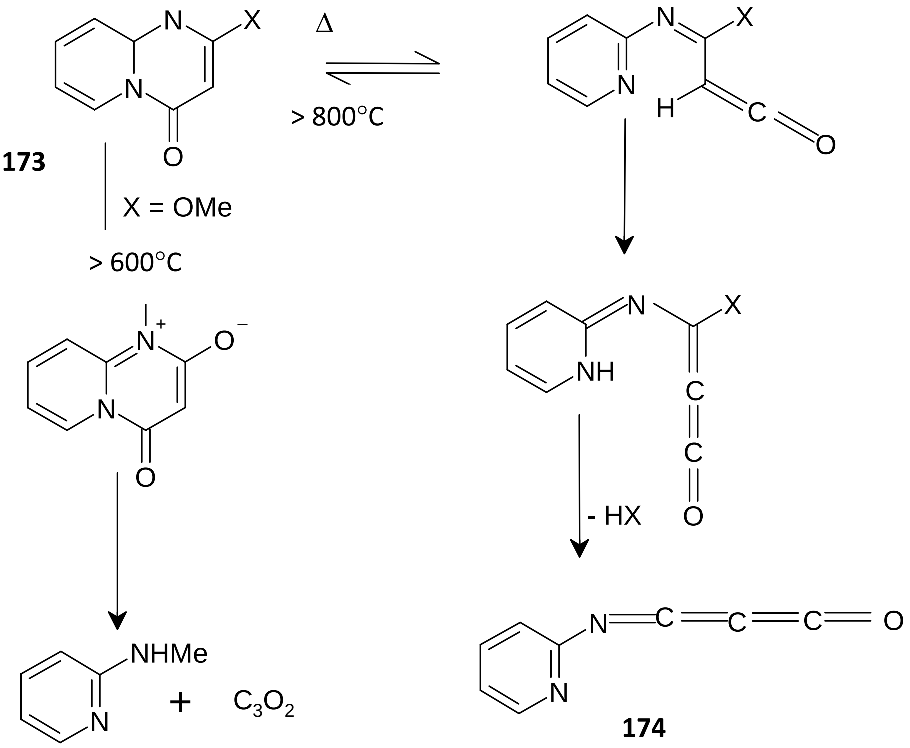
163

164

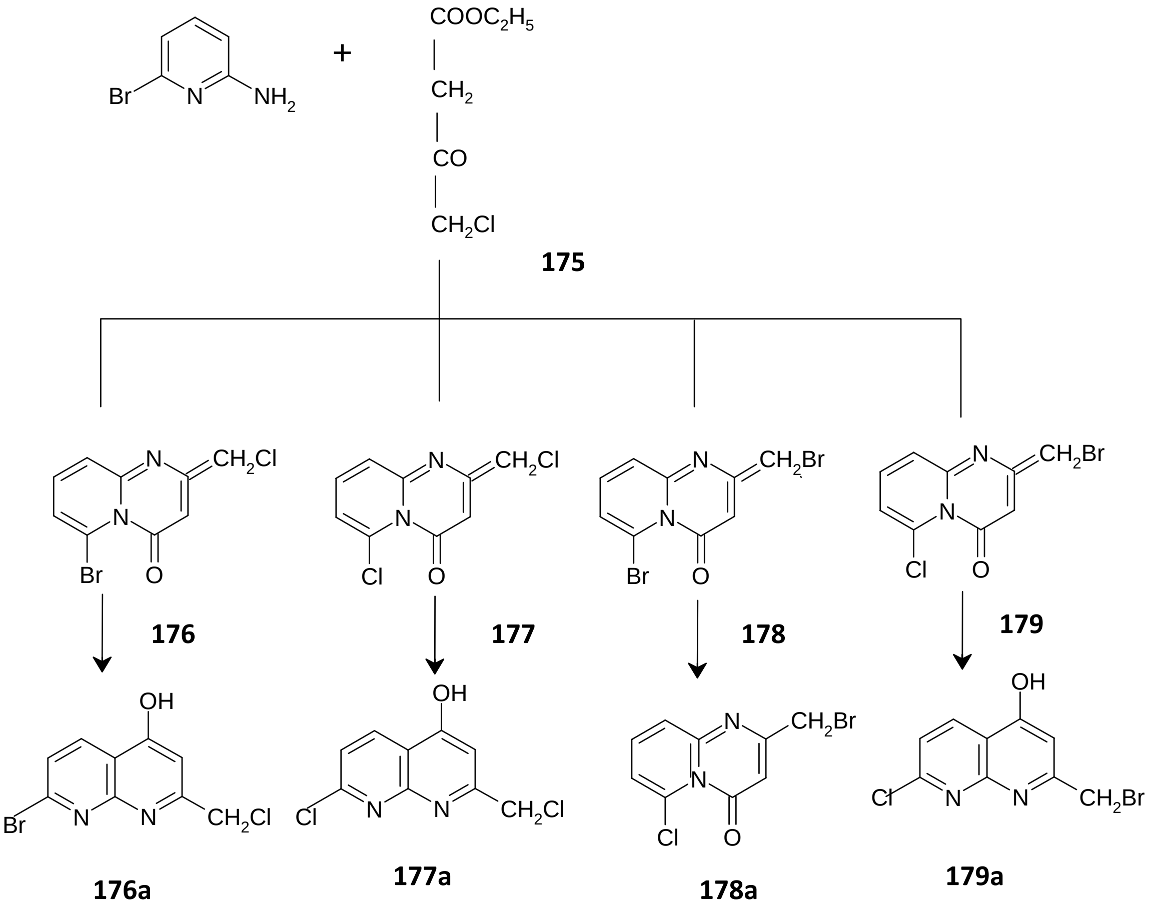
The flash vacuum thermolysis of 3-unsubstituted pyrimidinium olates **165** at 700°C, gave two fragments viz carbonsuboxide **166** and the corresponding substituted 2-aminopyridine **167,** while the 1,3-dimethyl pyrimidinylium olate **168** yielded, naphthyridone **169** at 700°C. N(1)-un substituted pryidopyrimidinones underwent **170** a cyclo reversion to afford 2-pyridyl isocyanate **171** and a ketene **172 (Anne Fiksdahl et al, 2000).**



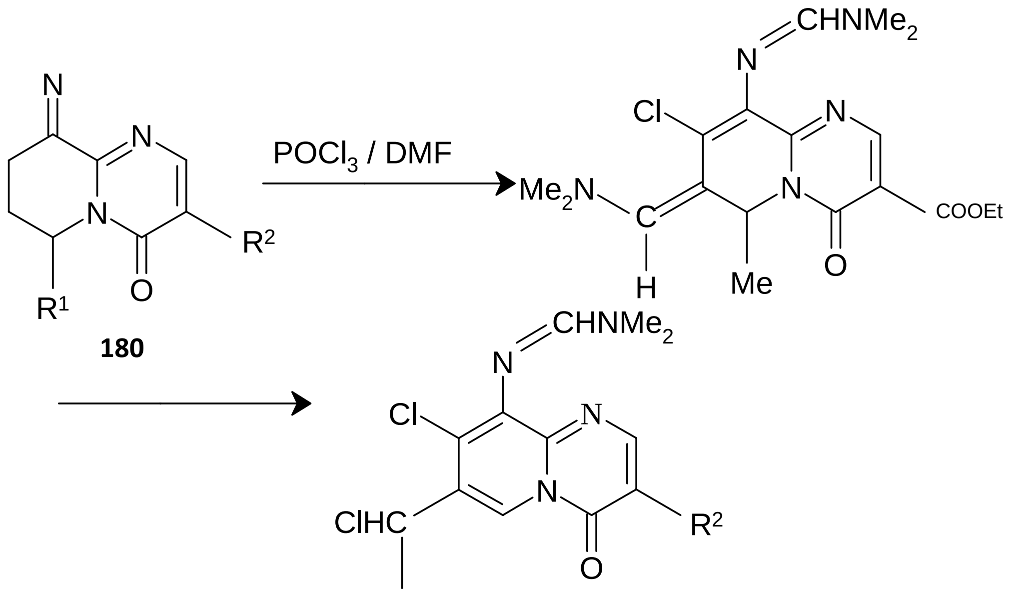
Flash vacuum Thermolysis (FVT) of 2-substituted-4H–pyrido[1,2-a] pyrimidin-4-ones **173** above 800°C afforded (2-Pyridyl) imino propadienone **174.** These reactions were interpreted in terms of reversible ring opening of 4H-pyrido[1,2-a]pyrimidin-4-ones to imidoyl-ketones **(Carsten Pluig et al, 1999).**



The condensation of 2-amino-6-bromo pyridine with ethyl 4-chloroacetacetate in PPA **175**, gave four possible dihalo-4H-pyrido [1,2-a] pyrimidin-4-ones **176, 177, 178, 179**. These pyrimidines on reflux with diphenyl, ether for several hours isomerised to the corresponding 1,8 naphthyridine derivatives **176a, 177a, 178a, 179a (Silvia Barontini et al, 1999).**



Under the conditions of Vilsmeier – Haack formylation, nitrogen bridgehead ring systems containing a 6,7,8,9-tetrahydro-4-H pyrido[1,2-a]pyrimidin-4-one moiety **180** underwent a ring transformation to afford the same nitrogen bridgehead ring systems containing an unsaturated 4H-pyrido [1,2-a]pyrimidin–4–one moiety **181**. The investigation of the ring transformation using deuterated and optically active derivatives showed the formation of 7-dimethylamino methylene-6,7-dihydro-4H-pyrido [1,2-a] pyrimidin–4–one species in the first step which is then transformed into unsaturated 4H–pyrido[1,2-a]pyrimidin–4–one moiety **(Istavan Hermecz et al, 1999).**

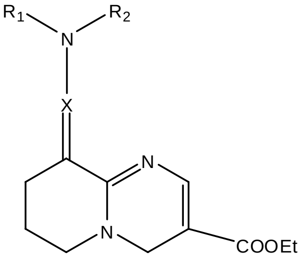


180

181

2.4. Physicochemical properties and structural studies

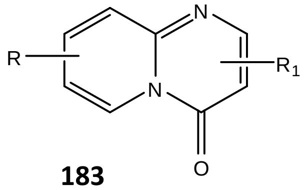
Protonation constants of some 9- substituted 4-oxo-6,7,8,9 tetrahydro-4H pyrido[1,2-a] pyrimidine-3-carboxylates **182** were determined by **Martin et al, (1985).**



182

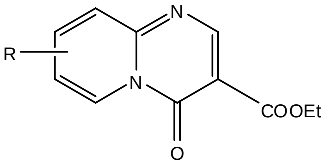
The saturation of the pyridine ring of the pyrido pyrimidines influences the pKa values only slightly The presence of a methyl group in position 9 renders protonation at the neighboring position N-1 sterically more difficult. Close linear correlations have been found between the protonation coefficients measured in water and in different mixtures of ethanol water **(Radeczky et al, 1985).**

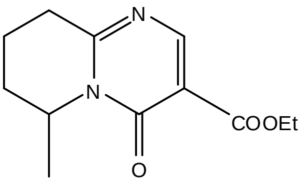
Hanko-Novak et al, (1984) determined protonation constants of 4-oxo-4H pyrido[1,2-a] pyrimidine-4-one **183**, its 6,7,8,9 –tetrahydro derivative and 2- and 3-phenyl derivatives by means of the Calvin “dml” potentiometric method in water and in ethanol-water solutions.



183

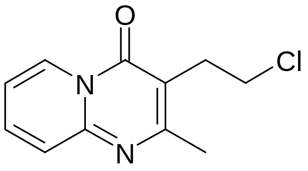
Hovath et al, (1974), carried out a spectrophotometric investigation of the protonation of 4-oxo-4H pyrido[1,2-a] pyrimidine-3-carboxylates **184 and 185** and acetates and proved that the portonation occurs at position N-1 of the bicycles.





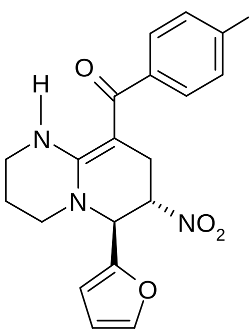
184 **185**

The crystal structure of 3-(2-Chloroethyl)-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidinium2,4,6-trinitrophenolate **186** was reported by **Jerry Jasinski et al, 2009.** In the compound the chloroethyl side chain is in a syn conformation, nearly orthogonal to the pyrimidine ring, with a dihedral angle of 88.5(1)^{0}8 between the plane of the chloroethyl chain and the pyrimidine ring. Extensive hydrogen-bond interactions occur between the cation–anion pair was observed.



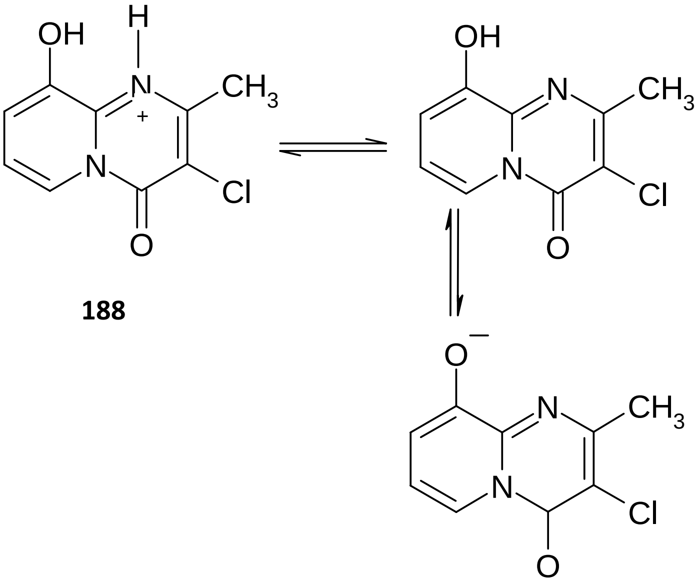
186

The crystal structure of (4-Fluorophenyl)[6-(2-furyl)-7-nitro-2,3,4,6,7,8-hexahydro-1H-pyrido[1,2-a]pyrimidin-9-yl]methanone **187** was studied by **Muhammad Yaqub et al, 2009.** In this compound the fused pyridine and pyrimidine rings adopt half-chair conformations. The structure displayed intramolecular N-H---O and intermolecular N-H---F hydrogen bonding.



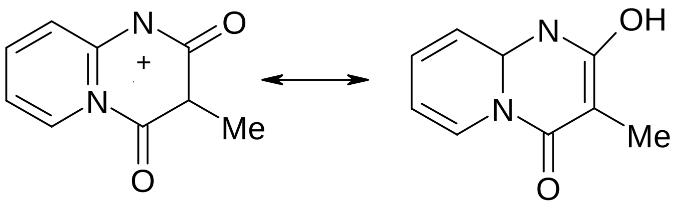
187

X ray diffraction studies of 2-methyl-3-chloro-9-hydroxypyrido [1,2–a]pyrimidin–4–onium perchlorae **188** were carried out by **Kovalchukova et al, (2004).** The studies revealed that the compound **188** exist in the molecular form in crystals and in the zwitter ion form in solutions. The investigation of series of pyrido[1,2-a]pyrimidines demonstrated that the tautomeric equilibrium in solution of compound of this class depends on the solvent type and pH of the medium.



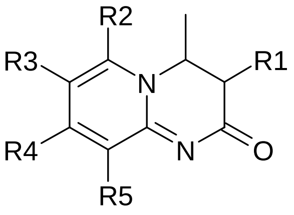
188

The X-ray crystal structures, ^{13}CNMR spectra and theoretical calculations (B3LYP16-31G*) for pyridopyrimidinylium ions showed that the compounds **189** exist in the mesoionic form in the crystal and in solution, but in the gas phase, their OH tautomers dominated as revealed by the Ar matrix IR spectra in conjunction with DFT calculations. From the X-ray crystal data it was concluded that the mesoionic compounds were intramolecular pyrindine-ketone zwitterions, with a high degree of positive charge on the pyridinium nitrogen **(Carsten Pliig et al, 2000).**

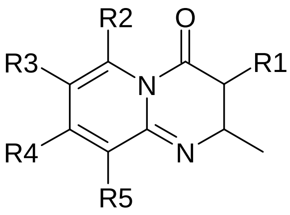


189

The unequivocal total assignment of ^{13}C and ^{1}H NMR spectra of some 4-methyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine **190** and 2-methyl-4-oxo-(4H)-pyrido[1,2-a]pyrimidine **191** derivatives were reported by **Krishnan Suri et al, 2003**.

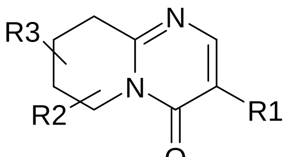


190



191

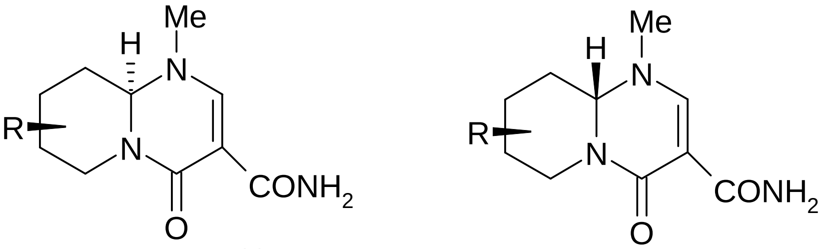
Conformational analysis of 6,7,8,9,-tetrahydro-4H pyrido[1,2-a]pyrimidin-4-ones **192** and their methyl derivatives were studied by NMR spectroscopy. The results showed that at room temperature the 6-methyl derivatives predominantly adopt the conformation with a pseudoaxial methyl group and 7-and 8 methyl derivatives with an equatorial methyl group, but the 9-methyl derivatives exist in essentially equally populated conformers **(Benjamin Podanyl et al, 1986).**



192

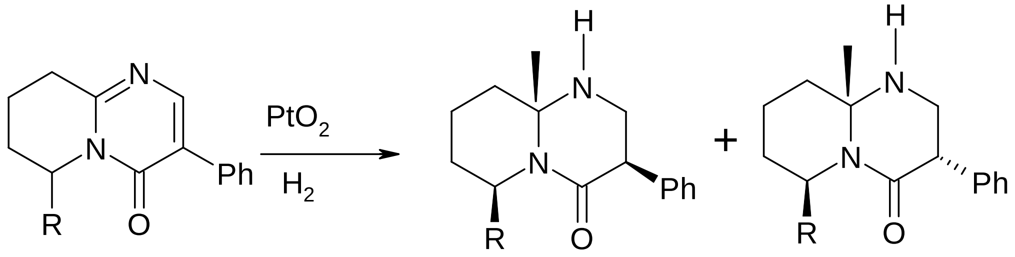
R_1 = COOEt/CH_2COOEt
R_2 = H,6-Me,7-Me,8-Me,9-Me
R_3 = H, 8-Me, 9-Me

Synthesis and stereochemistry of 4-oxo-1,6,7,8,9,9a-hexahydro-4H-pyrido [1,2-a]pyrimidine-3-carboxamides **193** were studied by **Istvan Hermecz 1985**.



trans **193** cis

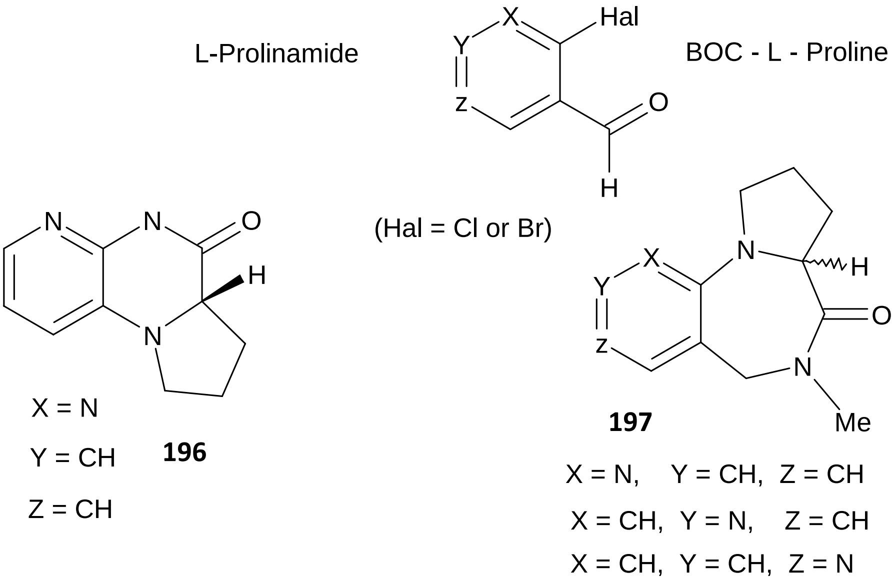
Catalytic hydrogenation of the tetrahydropyridopyrimidines **194** and the conformation of the resulting perhydro derivatives **195a and 195b** were reported by **Istvan Hermecz et al, 1982**.



194 **195a** **195b**

2.5. Pyrido-diazepine

Loreto Legeren et al, (2010), synthesized, pyrido(2,3-e)pyrrolo[1,2-a] (1-4)diazepin-10-one scaffold **196** by the alkylation of α-prolinamide with 3-(chloromethyl)-2-halopyridines, followed by cyclisation through an intramolecular Pd-catalysed amidation. Also they developed a synthetic route towards a diverse new pyrido(f)pyrrolo [1,2-a](1,4)-diazepin–7–ones, **197** by acylation of contiguously substituted (amino methyl) halo pyridines with BOC-L-proline followed by intra molecular amination.



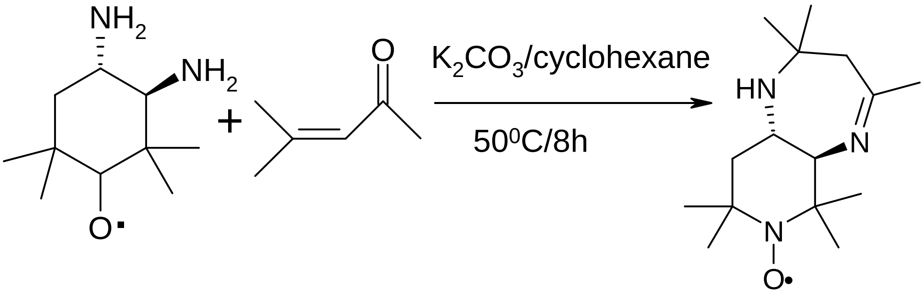
X = N
Y = CH
Z = CH

196

197

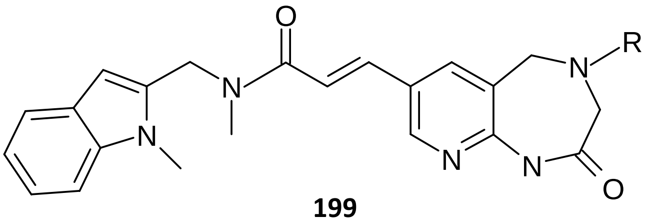
X = N, Y = CH, Z = CH
X = CH, Y = N, Z = CH
X = CH, Y = CH, Z = N

Synthesis and structure of trans-2,2,4,6,6,8,8-Heptamethyl-2,3,5a,6,7,8,9,9a–octahydro-1H–pyrido[4,3-b][1,4] diazepin-7-oxyl **198** were reported by **Sen et al, 2010.** According to the XRD data the radical has trans located substituents at thebridging bond of the bicycle.



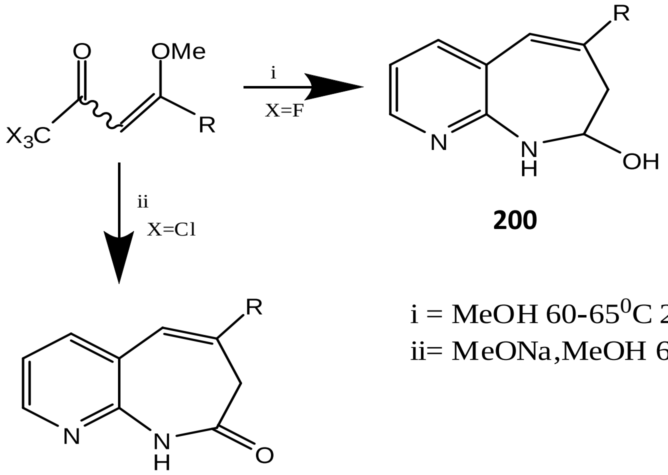
198

Jailall Ramnauth et al, 2009 reported 2,3,4,5-tetrahydro-1H-pyrido[2,3-b,e][1,4] diazepines **199** as inhibitors for the bacterial enoyl ACP reductase, FabI.



199

Heilo et al, (2007) reported the first synthesis of a series of 2-aryl(heteroaryl)-4-fluoromethyl-4,5-dihydro-3H-pyrido[2,3-b][1,4] diazepin-4-ols **200** by the direct condensation reaction of -4-methoxy-1,1,1 trifluoro alk-2-en-2ones with 2,3-dimaino pyridine in 54-57% yield. Another alternative and efficient route for the synthesis of a series of 2-aryl(heteroaryl)-4-3H-pyrido[2,3-b][1,4] diazepin-4(5H) ones **201** from the reaction of 4-methoxy1,1,1- tri chloro alk-3-3n3-2-ones with 2,3-diamino pyridine in 54-70% yield had also been reported by them.

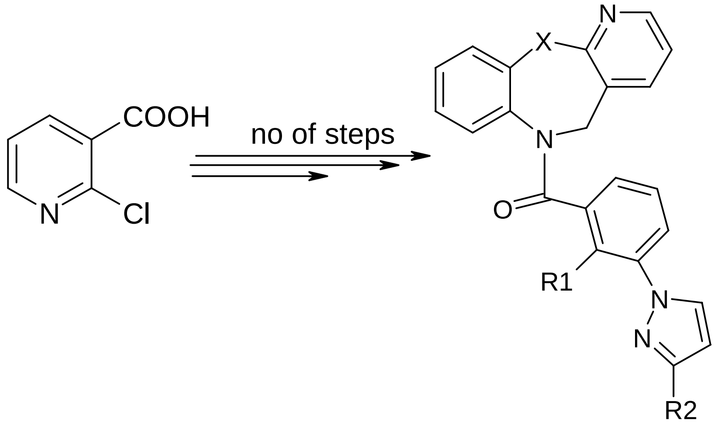


200

i = MeOH 60-65^{0}C 24h
ii= MeONa,MeOH 60-65^{0}C24h

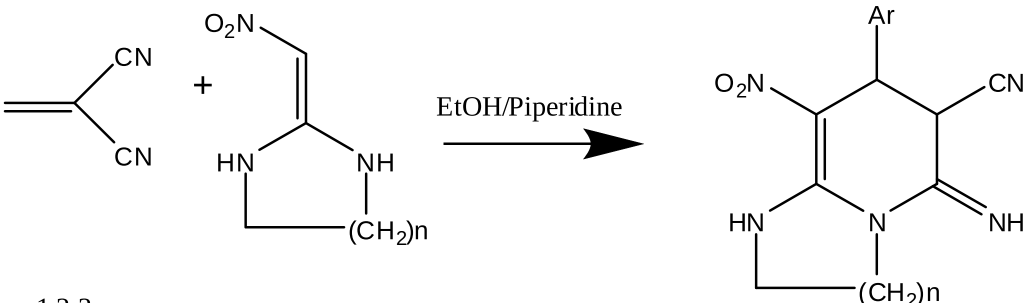
201

Pyrido benzodiazepines **202** was synthesized and reported to be a novel class of orally active, vasopressin V2 receptor selective agonists **(Amedeo Failli et al, 2006).**



202

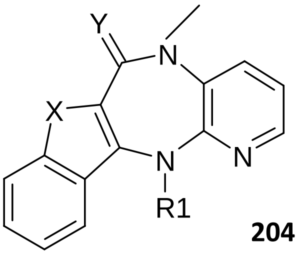
A new synthetic route oto polyfunctionally substituted imidazo[1,2-a] pyridines, pyrido[1,2-a]pyrimidines and pyrido[1,2-a]1,3diazepines **203** from the reactions of aryllidene malono nitriles with some nitroenamines was reported by **Hammouda et al, 2005.**



n=1,2,3

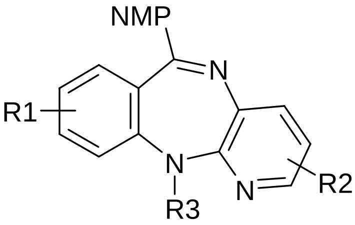
203

New arylpyrido-diazepine and thiodiazepine derivatives **204** were reported to be a potent and highly selective HIV-1 inhibitors by **Bellarosa et al, 1996.**

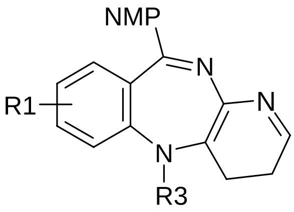


204

Jean-Francois Liegeois et al, 1993 reported the synthesis of a series of new N-methylpiperazinopyrido[2,3-b][1,4] **205** and [1,5] and pyrido[4,3-b][1,4]-and [1,5]-benzodiazepines **206**. These compounds were found to possess a high antipsychotic potential similar to that of well known antipsychotic agent clozapine.



205



206

MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1. GENERAL

Melting points were determined using Biochem melting point apparatus, and are uncorrected.

The infrared (IR) spectra were recorded in KBr pellet technique on a Perkin-Elmer spectrophotometer. Absorption frequencies are quoted in reciprocal centimeter.

Nuclear Magnetic Resonance (^{1}HNMR) spectra were determined by Bruker modern 400MHz and Bruker Avance 500MHz NMR instrument in D_2O, $CDCl_3$, MeOD and DMSO-d_6, with tetra methyl silane as internal reference. Chemical shift are quoted in parts per million (ppm) (s = singlet; d = doublet; t = triplet and m = multiplet).

Mass experiments were performed on GC (T 8000 TOP CE) and combined with mass spectrometer (Md 800 FIS ONS). Thin layer chromatography (TLC) was performed using glass plates coated with silica gel G to monitor and check the completion of each reaction.

Petroleum ether (60-80°C); ethyl acetate; ethyl alcohol were used as the developing solvents. Spots were detected with UV light and iodine. Anhydrous sodium sulfate was used to dry the solutions of organic extracts.

The solvents and reagents used for the synthesis were of reagent grade and were purified by standard methods. Purification of the crude products was carried out using chromatographic columns packed with silica gel.

In place where the preparation of a series of similar compounds is described and for the individual compound the quantity of the reactants as well as the reagents employed are indicated under each of them.

3.2. PREPARATION OF ACONIC ACID[207] [Campbell N.R and Hunt J.H 1947]

3.2.1. Preparation of Sodium aconate

Itaconic acid (260g) was powdered and stirred to a paste with water (340ml) in 5-litre beaker. Bromine (320g) was slowly added, keeping the temperature below 50˚C. When all but trace of bromine had disappeared, the solution was neutralized with sodium bicarbonate (336g). The mixture was then heated to 50˚ C on a water bath and treated with a suspension of anhydrous sodium carbonate (106g) in water (158ml) at 50˚C, added in small portions until the solution remained neutral. The mixture was cooled and allowed to remain at 0˚C for an hour. The crystalline sodium salt was collected by filtration, washed with a small amount of ice water and then with 95% alcohol and dried under vacuum.

3.2.2. Preparation of Aconic acid

Dry sodium aconate 100g was suspended in dry ether (300ml). Dry hydrogen chloride gas was then passed with stirring, until a gain in weight (30g) was obtained. The mixture was left over night; the solid (115g) was filtered off and extracted with ether in a soxhlet. Evaporation of the solvent gave the white crystals of aconic acid.

3.3. 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE ACETIC ACIDS

General Procedure[209a -h]

To a magnetically stirred solution of aconic acid (0.02mole) in alcohol, added drop wise the alcoholic solution of 2-amino pyridine (0.01mole) at room temperature. The precipitated solid was filtered, dried and was recrystallised from ethanol as colourless crystals.

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 2-aminopyridine: 1.88g; Ethanol: 50ml

Melting point : 221˚C, Yield - 4g (91%)

IR (γ) $_{\text{max:}}$ 2954 cm^{-1} (-OH), 1741 cm^{-1} (-CO), 1670 cm^{-1} (-CO), 1637 cm^{-1}(-CN), 1271 cm^{-1}, 985 cm^{-1}

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 3-methyl-2-aminopyridine: 2.38 g; Ethanol: 50ml; Melting point : 232˚C, Yield - 4.56g (96%)

IR (γ) $_{\text{max:}}$ 3010 cm^{-1} (-OH), 1748 cm^{-1} (-CO), 1666 cm^{-1} (-CO),1640 cm^{-1}(-CN), 1269 cm^{-1}, 983 cm^{-1}

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 4-methyl-2-aminopyridine: 2.38g; Ethanol: 50ml

Melting point : 233˚C, Yield - 4.4g (93%)

IR (γ) $_{\text{max:}}$ 3014 cm^{-1} (-OH), 1749 cm^{-1} (-CO), 1668 cm^{-1} (-CO), 1640 cm^{-1}(-CN), 1269 cm^{-1}, 983 cm^{-1}

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 5-methyl-2-aminopyridine: 2.38g; Ethanol: 50ml

Melting point : 233˚C, Yield - 4.1g (88%)

IR (γ) $_{\text{max:}}$ 3012 cm^{-1} (-OH), 1752 cm^{-1} (-CO), 1671 cm^{-1} (-CO), 1642 cm^{-1}(-CN), 1271 cm^{-1}, 980 cm^{-1}

2-oxo-6-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 6-methyl-2-aminopyridine: 2.38g; Ethanol: 50ml

Melting point : 234˚C, Yield - 3.88g (82%)

IR (γ) $_{\text{max:}}$ 2995 cm^{-1}(-OH), 1748 cm^{-1} (-CO), 1668 cm^{-1}, (-CO), 1640 cm^{-1}(-CN), 1270 cm^{-1}, 981 cm^{-1}

2-oxo-6,8-dimethyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 4,6-dimethyl-2-aminopyridine: 2.44g; Ethanol: 50ml

Melting point : 242˚C, Yield - 4.26g (85 %)

IR (γ) $_{max:}$ 2995 cm^{-1}(-OH), 1748 cm^{-1}(-CO), 1668 cm^{-1} (-CO), 1640 cm^{-1}(-CN), 1270 cm^{-1}, 981 cm^{-1}

2-oxo-5-bromo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 5-bromo-2-aminopyridine: 3.54g; Ethanol: 50ml

Melting point : 262-266˚C, Yield - 4.868g (79%)

IR (γ) $_{max:}$ 2990 cm^{-1}(-OH), 1750 cm^{-1}(-CO), 1670 cm^{-1} (-CO), 1644 cm^{-1}(-CN), 1271 cm^{-1}, 983 cm^{-1}, 710 cm^{-1}

2-oxo-5-bromo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylideneacetic acid

Aconic acid: 2.56g; 5-bromo-3-methyl-2-aminopyridine: 3.72g; Ethanol: 50ml;

Melting point: 265-267˚C, Yield - 4.8g (76%)

IR (γ) $_{max:}$ 3010 cm^{-1}(-OH), 1748 cm^{-1}(-CO), 1 668cm^{-1} (-CO), 1644 cm^{-1}(-CN), 1271 cm^{-1}, 983 cm^{-1}, 690 cm^{-1}

2-oxo-5-bromo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylideneacetic acid

Aconic acid: 2.56g; 5-bromo-3-methyl-2-aminopyridine: 3.72g; Ethanol: 50ml;

Melting point: 270-271˚C, Yield - 4.7g (70%).

IR (γ) $_{max:}$ 3010 cm^{-1}(-OH), 1748 cm^{-1}(-CO), 1668 cm^{-1}(-CO), 1644 cm^{-1}(-CN), 1271 cm^{-1}, 983 cm^{-1} , 690 cm^{-1}

2-oxo-5-bromo-6,8-dimethyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid

Aconic acid: 2.56g; 5-bromo-3-mehyl-2-aminopyridine: 3.72g; Ethanol: 50ml;

Melting point: 270-271˚C, Yield - 4.7g (70%).

IR (γ) $_{max:}$ 3012 cm^{-1}(-OH), 1750 cm^{-1}(-CO), 1667 cm^{-1} (-CO), 1645 cm^{-1}(-CN), 1272 cm^{-1}, 981 cm^{-1}, 694 cm^{-1}

3.4. PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONES

General Procedure[212a-e]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid and polyphosphoric acid was refluxed in a steam bath for 2-3hours under exclusion of moisture. Thereafter the reaction mixture was cooled and poured into crushed ice, and was neutralized with strong ammonia solution. A white precipitate settled down which was filtered and washed with ice cold water. The crude product thus obtained was dried and crystallized with pet ether to yield pure white needles.

Pyrido[1,2-a][1,3]diazepin-2(5H)-one

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid : 2.04g

polyphosphoric acid: 4g; Melting point: 136^0C; Yield - 1.1g (53%)

IR (γ) $_{max:}$ 1668 cm^{-1} (-CO), 1644 cm^{-1}(-CN), 1110 cm^{-1}

8-methyl-Pyrido[1,2-a][1,3]diazepin-2(5H)-one

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; polyphosphoric acid: 4g; Melting point: 139^0C; Yield - 1g (50%)

IR (γ) $_{max:}$ 1664 cm^{-1} (-CO), 1638 cm^{-1}(-CN), 1112 cm^{-1}

7-methyl-Pyrido[1,2-a][1,3]diazepin-2(5H)-one

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; polyphosphoric acid: 4g; Melting point: 137^0C; Yield - 1g (45%)

IR (γ) $_{max:}$ 1670 cm^{-1} (-CO), 1640 cm^{-1}(-CN), 1007 cm^{-1}

6-methyl-Pyrido[1,2-a][1,3]diazepin-2(5H)-one

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; polyphosphoric acid: 4g; Melting point: 136^0C; Yield - 1g (45%)

IR (γ) $_{max:}$ 1674 cm^{-1} (-CO), 1640 cm^{-1}(-CN), 1011 cm^{-1}

3.5. 3-METHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONES

General Procedure [213a-f]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid and acetic acid was refluxed in a steam bath for 2-3hours under exclusion of moisture. Thereafter the reaction mixture was cooled and poured into crushed ice, and was neutralized with strong ammonia solution. A white precipitate settled down which was filtered and washed with ice cold water. The crude product thus obtained was dried and crystallized with pet ether to yield pure white needles.

3-methyl-2H-pyrido[1,2-a]pyrimidin-2-one

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; Acetic acid: 10ml; Melting point: 128^0C; Yield - 1.3g (63%)

IR (γ) $_{max:}$ 1674 cm^{-1} (-CO), 1642 cm^{-1}(-CN)

3,9-dimethyl-2H-pyrido[1,2-a]pyrimidin-2-one

9-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; Acetic acid: 10ml; Melting point: 126^0C; Yield - 1.3g (59%)

IR (γ) $_{max:}$ 1678 cm^{-1} (-CO), 1639 cm^{-1}(-CN)

3,8 -dimethyl-2H-pyrido[1,2-a]pyrimidin-2-one

8-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; Acetic acid: 10ml; Melting point: 123^0C; Yield - 1g (46%)

IR (γ) $_{max:}$ 1680 cm^{-1} (-CO), 1640 cm^{-1}(-CN)

3,7-dimethyl-2H-pyrido[1,2-a]pyrimidin-2-one

8-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; Acetic acid: 10ml; Melting point: 125^0C; Yield - 1g (46%)

IR (γ) $_{max:}$ 1684 cm^{-1} (-CO), 1642 cm^{-1}(-CN)

3,6-dimethyl-2H-pyrido[1,2-a]pyrimidin-2-one

6-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; Acetic acid: 10ml; Melting point: 120^0C; Yield - 1g (46%)

IR (γ) $_{max:}$ 1678 cm^{-1} (-CO), 1639 cm^{-1}(-CN)

3,6,8-trimethyl-2H-pyrido[1,2-a]pyrimidin-2-one

4,6-dimethyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g; Acetic acid: 10ml; Melting point: 119^0C; Yield - 1g (46%)

IR (γ) $_{max:}$ 1676 cm^{-1} (-CO), 1638 cm^{-1}(-CN)

3.6. 2-ISOCYANATO-PYRIDINES

General Procedure [214a-c]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid and trifluoro acetic acid was refluxed in a steam bath for 2-3hours under exclusion of moisture. Thereafter the reaction mixture was cooled and poured into crushed ice, and was neutralized with strong ammonia solution. A white precipitate settled down which was filtered and washed with ice cold water. The crude product thus obtained was dried and crystallized with pet ether to yield pure white needles.

2-isocyanato-3-methylpyridine

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid : 2.18g

Trifluoro acetic acid: 10ml; Melting point: 121^{0}C; Yield - 0.9g (41%)

IR (γ) $_{max:}$ 1687 cm^{-1} (-CO), 1443 cm^{-1}(-CN), 1207 cm^{-1}

2-isocyanato-4-methylpyridine

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid : 2.18g

Trifluoro acetic acid: 10ml; Melting point: 119^{0}C ; Yield - 0.8g (36%)

IR (γ) $_{max:}$ 1629 cm^{-1} (-CO), 1449 cm^{-1}(-CN), 1110 cm^{-1}

2-isocyanato-5-methylpyridine

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid : 2.18g

Trifluoro acetic acid: 10ml; Melting point: 123^{0}C ; Yield - 0.8g (36%)

IR (γ) $_{max:}$ 1635 cm^{-1}, (-CO), 1458 cm^{-1}(-CN), 1110 cm^{-1}

3.7. ETHYL 2-(2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETATE

General Procedure [216 a -f]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid with ethanol (20ml) in presence of 5drops of H_2SO_4 and molecular sieves $40A^0$ was refluxed in a steam bath for 1-2hours. After the completion of the reaction the reaction mixture was poured into ice water, and neutralized with sodium bicarbonate. The precipitated solid was filtered, washed with water and dried. Since the ester obtained was highly insoluble in most of the solvents it was used as such for the further reactions without any purification.

Ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g

Ethanol: 50ml; H_2SO_4 : 5drops ; Melting point: 281-282^{0}C; Yield -2g (86%)

IR (γ) $_{max:}$ 1718 cm^{-1} (CO), 1676 cm^{-1}(-CO), 1612 cm^{-1}(-CN), 1147 cm^{-1}

Ethyl 2-(9-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

9-methyl- 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g

Ethanol: 50ml; H_2SO_4 : 5drops; Melting point: 287-289^{0}C; Yield - 2.1g (96%)

IR (γ) $_{max:}$ 1729 cm^{-1}(CO), 1633 cm^{-1}(-CO), 1600 cm^{-1}(-CN), 1110 cm^{-1}

Ethyl 2-(8-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

8-methyl- 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g

Ethanol: 50ml; H_2SO_4 : 5drops; Melting point: 287-289^{0}C; Yield - 2g (91%)

IR (γ) $_{max:}$ 1741 cm^{-1} (CO), 1623 cm^{-1}(-CO), 1610 cm^{-1}(-CN), 1121 cm^{-1}

Ethyl 2-(7-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

7-methyl- 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g

Ethanol: 50ml; H_2SO_4 : 5drops; Melting point: 287-289^{0}C; Yield - 2g (91%)

IR (γ) $_{max:}$ 1732 cm^{-1} (CO), 1657 cm^{-1}(-CO), 1628 cm^{-1}(-CN), 1121 cm^{-1}

Ethyl 2-(6-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

6-methyl- 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g

Ethanol: 50ml; H_2SO_4 : 5drops; Melting point: 287-289^{0}C; Yield - 2g (91%)

IR (γ) $_{max:}$ 1742 cm^{-1} (CO), 1647 cm^{-1}(-CO), 1645 cm^{-1}(-CN), 1133 cm^{-1}

3.8. 3-(2-HYDROXYETHYL)-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL

General Procedure-Method-I [217 a- e]

Sodium borohydride powder (6eq) was added to a stirred solution of ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate (1mM) in THF (50 ml). The resulting suspension was stirred at 0°C for 15 min. Methanol (50 ml) was then added drop wise during a period of 15 minutes with effervescence being observed. Stirring was maintained during a period of 15 to 60 minutes. After the end of reaction, the reaction mixture was quenched with a saturated solution of NH_4Cl (15ml) for further period of 1.5 hour The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 20 ml). The combined organic phase was dried (Na_2SO_4) and concentrated under low pressure to obtain a solid residue. The alcohols obtained were purified by column chromatography on silica gel, eluting with pet-ether to afford white crystals.

3-(2-hydroxyethyl)-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.27g; Sodium borohydride powder:20g; THF:50ml; Methanol: 50ml; NH_4Cl(saturated): 15ml; Melting point: 70-71^{0}C ; Yield - 0.65g (28%)

IR (γ) $_{max:}$ 3328 cm^{-1}(-OH), 2956 cm^{-1}(-NH), 1142 cm^{-1}, 1271 cm^{-1}

3-(2-hydroxyethyl)-9-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(9-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g Sodium borohydride powder: 20g; THF: 50ml; Methanol: 50ml; NH_4Cl(saturated): 15ml; Melting point: 79-81^{0}C ; Yield - 0.8g (31%)

IR (γ) $_{max:}$ 3335 cm^{-1}(-OH), 2982 cm^{-1}(-NH), 1156 cm^{-1}, 1267 cm^{-1},

3-(2-hydroxyethyl)-8-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(8-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g Sodium borohydride powder: 20g; THF: 50ml; Methanol: 50ml; NH_4Cl(saturated): 15ml; Melting point: 80-82^{0}C; Yield - 0.8g (31%)

IR (γ) $_{max:}$ 3328 cm^{-1}(-OH), 2988 cm^{-1}(-NH), 1144 cm^{-1}, 1274 cm^{-1}

3-(2-hydroxyethyl)-7-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(7-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g Sodium borohydride powder: 20g; THF: 50ml; Methanol: 50ml; NH_4Cl(saturated): 15ml; Melting point: 81-82^{0}C ; Yield - 0.7g (30%)

IR (γ) $_{max:}$ 3340 cm^{-1}(-OH), 2991 cm^{-1}(-NH), 1148 cm^{-1}, 1270 cm^{-1}

3-(2-hydroxyethyl)-6-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(6-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g Sodium borohydride powder: 20g; THF: 50ml; Methanol: 50ml; NH_4Cl(saturated): 15ml; Melting point: 80-83^{0}C ; Yield: 0.7g (30%)

IR (γ) $_{max:}$ 3344 cm^{-1}(-OH), 2994 cm^{-1}(-NH), 1159 cm^{-1}, 1268 cm^{-1}

General Procedure-Method-II

Sodium borohydride powder (6eq) was added to a stirred mixture of ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate (1mM), SDS(30g) and water (100ml). The resulting suspension was stirred at 0°C. Stirring was maintained during a period of 1hour. After the end of reaction, aqueous sodium perchlorate(1.1eq) was added to precipitate out the surfactant molecule as its perchlorate salt and filtered and the residue was washed thoroughly with water followed by a small amount of ether. The alcohols obtained were purified by column chromatography on silica gel, eluting with pet-ether to afford white crystals.

3-(2-hydroxyethyl)-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.27g.

Sodium borohydride powder: 20g; Water: 100ml; SDS:30g; Sodium perchlorate:15ml; Melting point: 70-71^{0}C ; Yield - 0.82g (36%)

3-(2-hydroxyethyl)-9-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(9-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Sodium borohydride powder: 20g; Water: 100ml; SDS: 30g; Sodium perchlorate: 15 ml; Melting point: 79-81^{0}C; Yield: 1.2g (45%)

3-(2-hydroxyethyl)-8-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(8-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Sodium borohydride powder: 20g; Water: 100ml; SDS: 30g; Sodium perchlorate: 15 ml; Melting point: 80-82^{0}C; Yield - 1.2g (45%)

3-(2-hydroxyethyl)-7-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(7-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Sodium borohydride powder: 20g; Water: 100ml; SDS: 30g; Sodium perchlorate :15 ml; Melting point: 81-82^{0}C; Yield - 1g (41%)

3-(2-hydroxyethyl)-6-methyl-2,3,4,9a-tetrahydro-1H-pyrido[1,2-a]pyrimidin-2-ol

Ethyl 2-(6-methyl2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Sodium borohydride powder: 20g; Water: 100ml; SDS: 30g; Sodium perchlorate: 15 ml; Melting point: 80-83^{0}C; Yield - 1g (41%)

3.9. 3-(2-HYDROXYETHYL)-9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

General Procedure [218a-e]

Lithium aluminium hydride powder (20g) was added to a stirred solution of ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate (1mM) in THF (75ml). The resulting suspension was stirred at 0°C for a period of 1-1.5 hours. After the end of reaction, the reaction mixture was quenched with a saturated solution of NH_4Cl (10ml) for further period of 1.5 hour The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 20 ml). The combined organic phase was dried (Na_2SO_4) and concentrated under low pressure to obtain a solid residue. The alcohols obtained were purified by column chromatography on silica gel, eluting with pet-ether to afford white crystals.

3-(2-hydroxyethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

Ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.27g

Lithium aluminium hydride powder: 20g; THF: 75ml; NH_4Cl(saturated): 10ml;

Melting point: 85-86^{0}C; Yield - 1.2g (52%)

IR $(\gamma)_{max:}$ 3250 cm^{-1}(-OH), 1718 cm^{-1}, 1628cm^{-1}(-CN)

3-(2-hydroxyethyl)-9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

Ethyl 2-(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Lithium aluminium hydride powder: 20g; THF: 75ml; NH_4Cl(saturated): 10ml;

Melting point: 90-91^{0}C; Yield - 1.3g (53%)

IR $(\gamma)_{max:}$ 3261 cm^{-1}(-OH), 1724 cm^{-1}, 1634cm^{-1}(-CN).

3-(2-hydroxyethyl)-8-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

Ethyl 2-(2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Lithium aluminium hydride powder: 20g; THF: 75ml; NH_4Cl(saturated): 10ml;

Melting point: 91-92^{0}C; Yield -1.25g (51%)

IR $(\gamma)_{max:}$ 3258 cm^{-1}(-OH), 1721 cm^{-1}, 1629cm^{-1}(-CN).

3-(2-hydroxyethyl)-7-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

Ethyl 2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Lithium aluminium hydride powder: 20g; THF: 75ml; NH_4Cl(saturated): 10ml;

Melting point: 91-92^{0}C; Yield -1.34g (55%)

IR $(\gamma)_{max:}$ 3254 cm^{-1}(-OH),1718 cm^{-1}, 1632cm^{-1}(-CN).

3-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

Ethyl 2-(2-oxo-6-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.44g

Lithium aluminium hydride powder: 20g; THF: 75ml; NH_4Cl(saturated): 10ml;

Melting point: 89-90^{0}C; Yield - 1.3g (53%)

IR (γ) $_{max:}$ 3252 cm^{-1}(-OH), 1722 cm^{-1}, 1636cm^{-1}(-CN).

3.10. (2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)-N-PHENYLACETAMIDES

General procedure [221a -f]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid (0.1mole) and purified thionyl chloride (0.20mole) was stirred at room temperature under exclusion of moisture till the solution was complete. The excess thionyl chloride was distilled off under reduced pressure. The residue was taken up in anhydrous ether (25ml) and gradually added to a well cooled and stirred mixture of aniline (0.02mole) in dry ether (25ml).After the addition was over it was set aside for a few minutes and then poured into ice water. The precipitated solid was filtered, dried and purified by column chromatography.

(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-phenylacetamides

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g

Thionyl chloride: 7ml; Aniline: 2.5g; Ether: 50ml; Melting point: 228-230^{0}C; Yield -3g (66%)

IR (γ) $_{max:}$ 3010 cm^{-1}(-NH), 1722 cm^{-1}(-CO), 1690 cm^{-1} (-CO)

(**2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-p-tolylacetamide**

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g

Thionyl chloride: 7ml; p-toludine: 2.7g; Ether: 50ml; Melting point: 249-251^{0}C; Yield - 2.8g (59%)

IR (γ) $_{max:}$ 3016 cm^{-1}(-NH), 1728 cm^{-1}(-CO), 1688 cm^{-1} (-CO)

N-(4-methoxyphenyl)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g

Thionyl chloride: 7ml; p-anisidine: 3.1g; Ether: 50ml; Melting point: 245-246^{0}C; Yield - 3.1g (62%)

IR (γ) $_{max:}$ 3018 cm^{-1}(-NH), 1730 cm^{-1}(-CO), 1691 cm^{-1} (-CO)

N-(4-chlorophenyl)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g

Thionyl chloride: 7ml; p-chloro-aniline: 3.2g; Ether: 50ml; Melting point: 257-258^{0}C; Yield - 3.5g (67%)

IR (γ) $_{max:}$ 3110 cm^{-1}(-NH), 1758 cm^{-1}(-CO), 1672 cm^{-1} (-CO)

(N-(2,5-dimethoxyphenyl)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g.

Thionyl chloride: 7ml; 2,5-dimethoxy-aniline: 3.8g; Ether: 50ml; Melting point: 267-278^{0}C; Yield - 3.2g (55%)

IR (γ) $_{max:}$ 3114 cm^{-1}(-NH), 1760 cm^{-1}(-CO), 1664 cm^{-1} (-CO)

N-benzyl-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g.

Thionyl chloride: 7ml; Benzylamine: 2.6g; Ether: 50ml; Melting point: 272-273^{0}C; Yield - 3g (64%)

IR (γ) $_{max:}$ 3010 cm^{-1}(-NH), 1731 cm^{-1}(-CO), 1691 cm^{-1} (-CO).

(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-phenylacetamides

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g.

Thionyl chloride: 7ml; Aniline: 2.5g; Ether: 50ml; Melting point: 232-234^{0}C; Yield - 3.1g (66%)

IR (γ) $_{max:}$ 3121 cm^{-1}(-NH), 1736 cm^{-1}(-CO), 1661 cm^{-1} (-CO)

(**2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-p-tolylacetamide**

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g.

Thionyl chloride: 7ml; p-toludine: 2.7g; Ether: 50ml; Melting point: 252-253^{0}C; Yield - 3g (61%)

IR (γ) $_{max:}$ 3110 cm^{-1}(-NH), 1769 cm^{-1}(-CO), 1668 cm^{-1} (-CO)

N-(4-methoxyphenyl)-2-(2-oxo7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g.

thionyl chloride: 7ml; p-anisidine:3.1g; Ether: 50ml; Melting point: 248-250^{0}C; Yield - 3.2g (60%)

IR (γ) $_{max:}$ 3020 cm^{-1}(-NH), 1734 cm^{-1}(-CO), 1691 cm^{-1} (-CO)

N-(4-chlorophenyl)-2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g. Thionyl chloride:7ml; p-chloro-aniline: 3.2g; Ether: 50ml; Melting point: 262-263^{0}C; Yield - 3.6g (67%)

IR (γ) $_{max:}$ 3014 cm^{-1}(-NH), 1741 cm^{-1} (-CO), 1684 cm^{-1} (-CO)

(N-(2,5-dimethoxyphenyl)-2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g. Thionyl chloride: 7ml; 2,5-dimethoxy-aniline: 3.8g; Ether: 50ml; Melting point: 269-271^{0}C; Yield - 3.3g (56%)

IR (γ) $_{max:}$ 3020 cm^{-1}(-NH), 1742 cm^{-1}(-CO), 1691 cm^{-1} (-CO)

N-benzyl-2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid:2.18g. Thionyl chloride: 7ml; Benzylamine: 2.6g; Ether: 50ml; Melting point: 274-275^{0}C; Yield - 3g (62%)

IR (γ) $_{max:}$ 3110 cm^{-1}(-NH), 1742 cm^{-1}(-CO), 1678 cm^{-1} (-CO)

(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-phenylacetamides

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid:2.18g. Thionyl chloride: 7ml; Aniline: 2.5g; Ether: 50ml; Melting point:234-235^{0}C; Yield - 3.1g (66%)

IR (γ) $_{max:}$ 3114 cm^{-1}(-NH), 1760 cm^{-1}(-CO), 1664 cm^{-1} (-CO)

(**2-(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-p-tolylacetamide**

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g. Thionyl chloride: 7ml; p-toludine: 2.7g; Ether: 50ml; Melting point: 254-255^{0}C; Yield - 3g (61%)

IR (γ) $_{max:}$ 3121 cm^{-1}(-NH), 1752 cm^{-1}(-CO), 1654 cm^{-1} (-CO)

N-(4-methoxyphenyl)-2-(2-oxo9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g. Thionyl chloride: 7ml; p-anisidine: 3.1g; Ether: 50ml; Melting point: 249-250^{0}C; Yield - 3.2g (60%)

IR (γ) max: 3012 cm^{-1}(-NH), 1777 cm^{-1}(-CO), 1646 cm^{-1} (-CO)

N-(4-chlorophenyl)-2-(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g. Thionyl chloride: 7ml; p-chloro-aniline: 3.2g; Ether: 50ml; Melting point: 263-264^{0}C; Yield - 3.6g (67%)

IR (γ) max: 3110 cm^{-1}(-NH), 1742 cm^{-1}(-CO), 1678 cm^{-1} (-CO)

(N-(2,5-dimethoxyphenyl)-2-(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g. Thionyl chloride: 7ml; 2,5-dimethoxy-aniline: 3.8g; Ether: 50ml; Melting point : 269-272^{0}C; Yield - 3.3g (51%)

IR (γ) max: 3110 cm^{-1}(-NH), 1758 cm^{-1}(-CO), 1668 cm^{-1} (-CO)

N-benzyl-2-(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid:2.18g. Thionyl chloride: 7ml; Benzylamine: 2.6g; Ether: 50ml; Melting point: 275-276^{0}C; Yield - 3g (62%)

IR (γ) max: 3118 cm^{-1}(-NH), 1768 cm^{-1}(-CO), 1672 cm^{-1} (-CO)

3.11. (5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE)-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONES

General Procedure [223a-e] [Jumat Salimon et al., 2010]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid, thiosemicarbazide and phosphorous oxy chloride (5ml) was refluxed gently in a steam bath for 3hours under exclusion of moisture. After cooling, water was added (50ml). The mixture was refluxed for 3hours and filtered. The filtrate was neutralized with sodium bicarbonate. The precipitate was filtered and washed with ice cold water and crystallized from alcohol.

(5-amino-1,3,4-thiadiazol-2-yl)methylene)-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g.
Thiosemicarbazide: 1g; Phosphorous oxy chloride: 5ml; Melting point: 170-171^{0}C; Yield - 1.7g (56%)

IR (γ) $_{max:}$ 3315cm^{-1} (NH_2), 1694cm^{-1}(-CO), 1545 cm^{-1}(C=N), 637cm^{-1}(C=S)

(5-amino-1,3,4-thiadiazol-2-yl)methylene)-9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid:2.18g.
Thiosemicarbazide: 1g; Phosphorous oxy chloride: 5ml; Melting point: 174-176^{0}C; Yield - 1.8g (56%)

IR (γ) $_{max:}$ 3324cm^{-1} (NH_2), 1710cm^{-1}(-CO), 1565 cm^{-1}(C=N), 634cm^{-1}(C=S)

(5-amino-1,3,4-thiadiazol-2-yl)methylene)-8-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid:2.18g.
Thiosemicarbazide: 1g; Phosphorous oxy chloride: 5ml; Melting point:173-174^{0}C; Yield - 1.8g (56%)

IR (γ) $_{max:}$ 3367cm^{-1} (NH_2), 1708cm^{-1}(-CO), 1556 cm^{-1}(C=N), 648cm^{-1}(C=S)

(5-amino-1,3,4-thiadiazol-2-yl)methylene)-7-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g.
Thiosemicarbazide: 1g; Phosphorous oxy chloride: 5ml; Melting point:175-176^{0}C; Yield - 1.5g (42%).

IR (γ) $_{max:}$ 3310cm^{-1} (NH_2), 1698cm^{-1}(-CO), 1574 cm^{-1}(C=N), 645cm^{-1}(C=S)

(5-amino-1,3,4-thiadiazol-2-yl)methylene)-6-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one

2-oxo-6-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g Thiosemicarbazide: 1g; Phosphorous oxy chloride: 5ml; Melting point: 173-175^{0}C; Yield -1.6g (50%)

IR (γ) $_{max:}$ 3342cm^{-1} (NH_2), 1710cm^{-1}(-CO), 1576 cm^{-1}(C=N), 657 cm^{-1}(C=S)

3.12. ETHYL 2-(2-THIOXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETATE

General Procedure[224a-c]

A mixture of ethyl 2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate, pyridine and P_4S_{10} (1eq) were heated under reflux in a steam bath under exclusion of moisture for 30 – 60 minutes. Solvent was removed under vacuum and the reaction mixture was poured into crushed ice; the precipitated solid was filtered, washed with ice cold water. The products obtained were purified by column chromatography on silica gel, eluting with pet-ether-ethyl acetate (3:1) mixture to afford pale yellow crystals.

Ethyl 2-(9-methyl-2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

2-(2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.18g

Pyridine: 5ml; P_4S_{10}: 5g; Melting point: 168-170^{0}C; Yield - 1.2g (55%)

IR (γ) $_{max:}$ 1190cm^{-1}(C=S), 1050 cm^{-1}, 935 cm^{-1}

Ethyl 2-(8-methyl-2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

2-(2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.18g Pyridine: 5ml; P_4S_{10}:5g; Melting point: 169-171^{0}C; Yield -1.3g (59%)

IR (γ) $_{max:}$ 1180cm^{-1}(C=S), 1030 cm^{-1}, 925 cm^{-1}

Ethyl 2-(7-methyl-2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate

2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate: 2.18g

Pyridine: 5ml; P_4S_{10}: 5g; Melting point: 168-169^{0}C; Yield - 1.2g (55%)

IR (γ) $_{max:}$ 1140cm^{-1}(C=S), 1035 cm^{-1}, 900 cm^{-1}

3.13. BENZYL 2-(2-THIOXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)YLIDENE)ETHANEDITHIOATE

General Procedure[225a-d]

A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid, benzyl alcohol and P_4S_{10} (2eq) in toluene (100ml) was refluxed for 2hours in a steam bath under exclusion of moisture. A dark red colour was developed immediately after heating. After the reaction was complete, it was cooled to room temperature, solvent was removed under vacuum and the residue was purified by re-crystallization with alcohol.

Benzyl -2-(2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)ylidene)ethanedithioate

2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.04g; Benzyl alcohol: 2.16g; P_4S_{10}: 8g; Toluene: 100ml; Melting point: 162-163^{0}C; Yield - 1.8g (41%)

IR (γ) $_{max:}$ 1252cm^{-1}(C=S), 1187 cm^{-1}(C=S), 1043 cm^{-1}, 925 cm^{-1}

Benzyl-2-(9-methyl-2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)ethanedithioate

2-oxo-9-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g benzyl alcohol: 2.16g; P_4S_{10}: 8g; Toluene: 100ml; Melting point:168-169^{0}C; Yield - 2.2g (50%)

IR (γ) $_{max:}$ 1232cm^{-1}(C=S), 1174 cm^{-1}(C=S), 1051 cm^{-1}, 945 cm^{-1}

Benzyl-2-(8-methyl-2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)ethanedithioate

2-oxo-8-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g Benzyl alcohol: 2.16g; P_4S_{10}: 8g; Toluene: 100ml; Melting point: 169-170^{0}C; Yield - 2.3g (52%)

IR (γ) $_{max:}$ 1242cm^{-1}(C=S), 1190 cm^{-1}(C=S), 1032 cm^{-1}, 985 cm^{-1}

Benzyl-2-(7-methyl-2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)ethanedithioate

2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid: 2.18g Benzyl alcohol: 2.16g; P_4S_{10}: 8g; Toluene: 100ml; Melting point: 169-170^{0}C; Yield: 2g(45%)

IR (γ) $_{max:}$ 1253cm^{-1}(C=S), 1180 cm^{-1}(C=S), 1052 cm^{-1}, 945 cm^{-1}

3.14. ANTIBACTERIAL STUDY OF THE COMPOUNDS

Sensitivity Studies

Procedure

Preparation of inoculums

The inoculums for the experiment were prepared in fresh Nutrient broth from preserved slant culture. The inoculums were standardized by adjusting the turbidity of the culture to that of McFarland standards. The turbidity of the culture was adjusted by the addition of sterile saline or broth (if excessive or by further incubation to get required turbidity.

Preparation of Sterile swabs

Cotton wool swab on wooden applicator or plastics were prepared and sterilized by autoclaving or dry heat (only for wooden swabs) by packing the swabs in culture tubes, papers or tins etc.

Sterilization of forceps

Forceps were sterilized by dipping in alcohol and burning off the alcohol

Experiment

The standardized inoculums was inoculated in the plates prepared earlier (aseptically) by dipping a sterile in the inoculums removing the excess of inoculums by passing by pressing and rotating the swab firmly against the side of the culture tube above the level of the liquid and finally streaking the swab all over the surface of the medium 3 times rotating the plate through an angle of 60^0C after each application. Finally passed the swab round the edge of the agar surface. Left the inoculums to dry at room temperature with the lid closed.

Each Petri dish was divided into 4 quadrants, in 3 quadrants extract discs such as I (100mcg), II (200mcg), III (300mcg) discs (discs are soaked overnight in extract solution) and one quadrant for Standard Ciprofloxacin 5mcg, were placed in each quadrant with the help of sterile forceps. Then petri dishes were placed in the refrigerator at 4^0C or at room temperature for 1 hour for diffusion. Incubate at 37^0C for 24 hours. Observed the zone of inhibition produced by different Antibiotics. Measured it using a scale or divider or verneir callipers and recorded the average of two diameters of each zone of inhibition.

3.15. IN VITRO ANTICANCER SCREENING

The human cervical cancer cell line (**HeLa**), Human laryngeal epithelial carcinoma cells (**HEp-2**) and **NIH 3T3** mouse embryonic fibroblasts were obtained from National Centre for Cell Science (NCCS), Pune. The HeLa and HEp-2 cells were grown in Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS) and NIH 3T3 fibroblasts were grown in Dulbeccos Modified Eagles Medium (DMEM) containing with 10% FBS.

For screening experiment, the cells were seeded into 96-well plates in 100µl of respective medium containing 10% FBS, at plating density of 10,000 cells/well and incubated at 37^0C, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to addition of extracts. The extracts were solubilized in Dimethylsulfoxide and diluted in respective medium containing 1% FBS. After 24 h, the medium was replaced with respective medium with 1% FBS containing the extracts at various concentration (eg; 6.25, 12.5, 25, 50 µg/ml etc…) and incubated at 37^0C, 5% CO2, 95% air and 100% relative humidity for 48h. Triplicate was maintained and the medium containing without extracts were served as control.

After 48h, 10µl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37^0C for 4h. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100 µl of DMSO and then measured the absorbance at 570 nm using micro plate reader.

The % cell inhibition was determined using the following formula and graph was plotted between % Cell inhibition and concentration and from this IC50 was calculated.

% cell Inhibition = 100- Abs (drug)/Abs (control) x100.

RESULTS AND DISCUSSION

4. RESULTS AND DISCUSSION

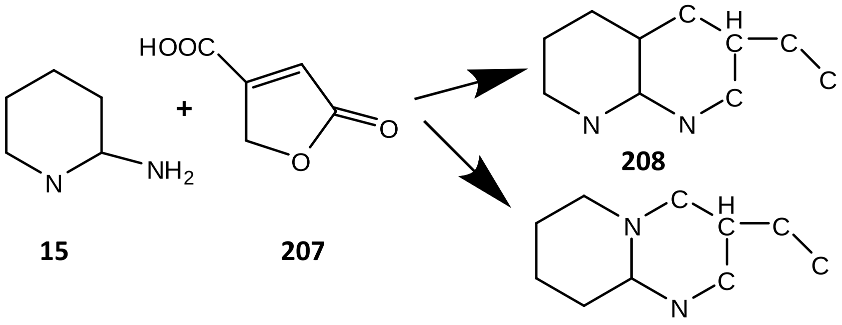
The results pertaining to the study of "Synthesis, Reactions and Biological Activity of Functionalized Pyrido[1,2-a]Pyrimidin-2-Ones" are discussed below:

The condensation of various anilines with aconic acid **207** had been successful in the synthesis of 2-quinolone-3-acetic acids which were precursors for the synthesis of furo, thieno, selenolo, tellurolo and pyrrolo [2,3-b] quinolines. **(Shanmugam et al, 1973).** Hence it was thought to adapt a similar method for the preparation of pyridopyrimidine acetic acids employing 2-aminopyridines instead of anilines with aconic acid.

2-amino pyridine **15** might cyclise in two ways

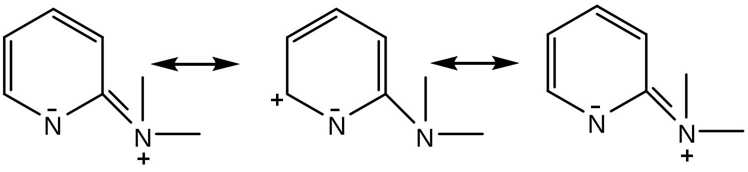
(i) One leading to the formation of 1,8 naphthyridines **208**

(ii) The other leading to the formation of pyrido pyrimidines.**209**



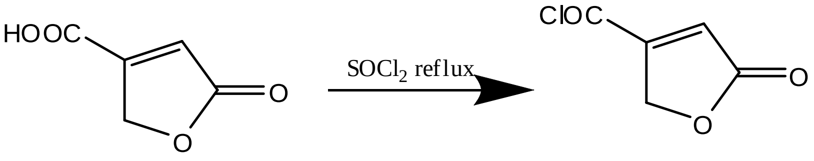
15 **207** **208** **209**

The formation of pyrimidines is not surprising since resonance structure **210a,** which may be considered as an activated form leading to pyrimidines, probably contributes considerably to the structure of the 2-amino pyridine derivative. This resonance structure makes the main contribution to the structure of 2-aminopyridine itself **(Charles et al, 1949).**



210a **210b** **210c**

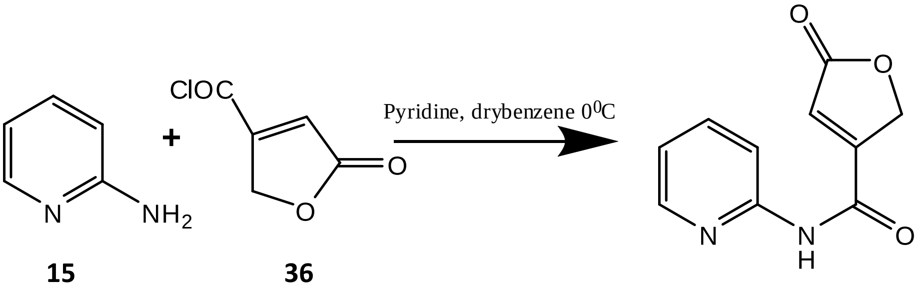
To achieve the objective, attempts were made to prepare aconamides from aconic acid. (i) Firstly aconic acid **207** was converted into aconyl chloride **36** by refluxing with thionyl chloride.



207 **36**

Scheme - 1

A dark brown liquid was obtained which was subsequently treated with 2-aminopyridine which was expected to yield N-(α-pyridylacondamide) **208**.

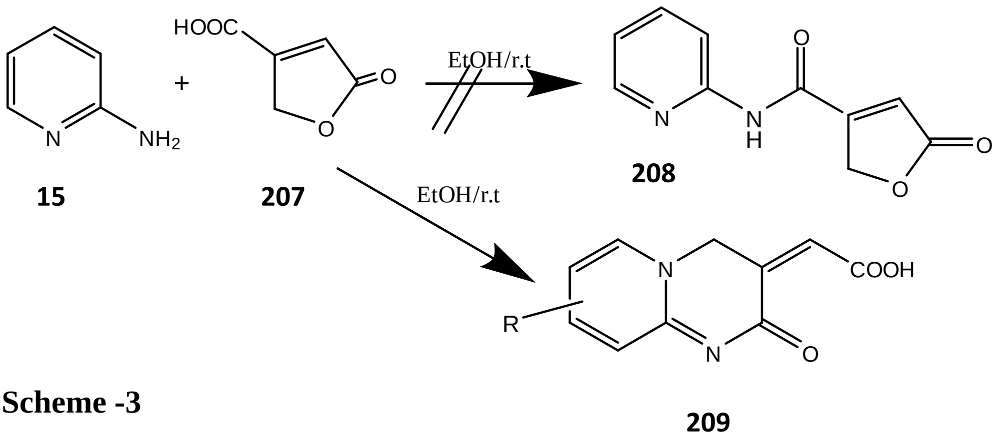


15 **36** **208**

Scheme - 2

But the reaction yielded a sticky brown residue which was unisolable. Since the attempts to synthesize aconamide from aconyl chloride were unsuccessful, condensation of aconic acid with 2-amino pyridine in presence of alcohol was tried.

The reaction was carried out by adding slowly the solution of 2-amino pyridine **15** in ethanol to a magnetically stirred suspension of aconic acid **207** in ethanol. The reaction proceeded spontaneously in alcohol at room temperature and was complete within few hours with excellent yields.



Scheme -3

R = H, 3-methyl, 4-methyl, 5-methyl, 6-methyl, 4,6-dimethyl,5-bromo, 3-methyl-5-bromo, 5--bromo 4-methyl, 4,6-dimethyl-5-bromo,5-nitro,3-methyl-5-nitro.

The formation of the cyclized product **209** was evidenced by the IR spectrum which exhibited a strong intense band at 1670 cm^{-1} and1637 cm^{-1} due to the C=O and C=N of pyrido pyrimidinone nucleus. A broad intense O-H stretching band at 3300 cm^{-1} - 2600 cm^{-1} centered at 2954 cm^{-1} was also observed which is overriding spectral feature of the carboxylic acid. This was also confirmed by the presence of strong intense O-H in plane bend at 1394 cm^{-1}along with medium intense O-H out of plane bend at 985cm^{-1}. The strong and medium intense bands at 1741 cm^{-1} and 1271 cm^{-1} were attributed to the -C=O and -C-O stretch of the carboxylic acid moiety respectively. The absence of N-H in plane bend at 1570 - 1515 cm^{-1} and N-H out of plane bend at 750 - 680 cm^{-1} also confirms that the product formed was **209** and not **208.**

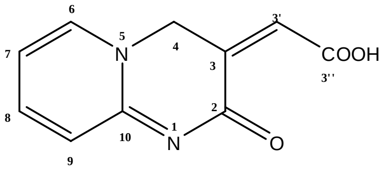
Analysis of the NMR spectrum of the compound **209a** revealed six signals for protons at δ 5.00, 6.3, 6.8, 6.9, 7.7, 7.8 and ten signals for carbon at δ 73, 112, 113, 122, 134, 144, 153, 164, 167, 177 **(Figures-1 and 2).** DEPT-135 (**Figure-3)** spectrum showed the presence of five methine carbons and one methylene carbon. Hence the remaining four carbons must be quaternary which was in accordance with the proposed structure **209.**

The complete structural analysis was made through ^{1}H, ^{13}C NMR spectrum, and 2D NMR - COSY, HETCOR and HMBC **(Figures-4, 5** and **6)** measurements. For the compound 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid **209** the signal at δ 7.8 was assigned to C_6-H, since it is deshielded by the neighboring nitrogen. C_7 proton and C_9 proton appeared at δ 6.8 and 6.9 as triplet and doublet respectively because they experience shielding effect by virtue of the position and nature of bonding **(Hikmat N. Al-Jallo et al, 1978).** The signal for proton at C_8 appeared as doublet at δ 7.7. The protons resonating at δ 6.3 and δ 5.0 were due to C_3-H and C_4-H.

The ^{13}C signals were assigned using HETCOR. The signals of carbon at δ 73, 122, 112, 113, 134 and 144 correlated with the proton signals at δ 5.00, 6.3, 6.8, 6.9, 7.7 and 7.8 respectively. The proton and carbon assignments are given in **Table-1**. The positions of the quaternary carbons were assigned using HMBC spectrum. The signals at δ 164 and 167 showed correlation with the exocyclic methine proton. Hence δ 167 was assigned to the carboxyl carbon and the signal at δ 164 to C_{10}. A long range ^3J coupling was observed between C_4-H and exocyclic methine (C_3') in the COSY spectrum. Other correlations observed in the COSY spectrum of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid are given in the **Figure-7.** The HMBC correlations are given in **Table-2** and **Figure-8.**

TABLE -1

NMR DATA OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



^1H Shift in ppm	Multip-licity/ no. of ^1H	Hydrogen	C^{13} shift in ppm	Carbon	Dept-135	C^{13} shift in ppm	Carbon	Dept-135
6.3	d/1	H_3'	177	C_2	-C	112	C_7	-CH
5.00	s/2	H_4	164	C_3	-C	134	C_8	-CH
7.8	t/1	H_6	122	C_3'	-CH	113	C_9	
6.8	t/1	H_7	167	C_3''	-C	153	C_{10}	
7.7	d/1	H_8	73	C_4	$-CH_2$			
6.9	d/1	H_9	144	C_6	-CH			

TABLE – 2

HMBC CORRELATIONS OBSERVED IN 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

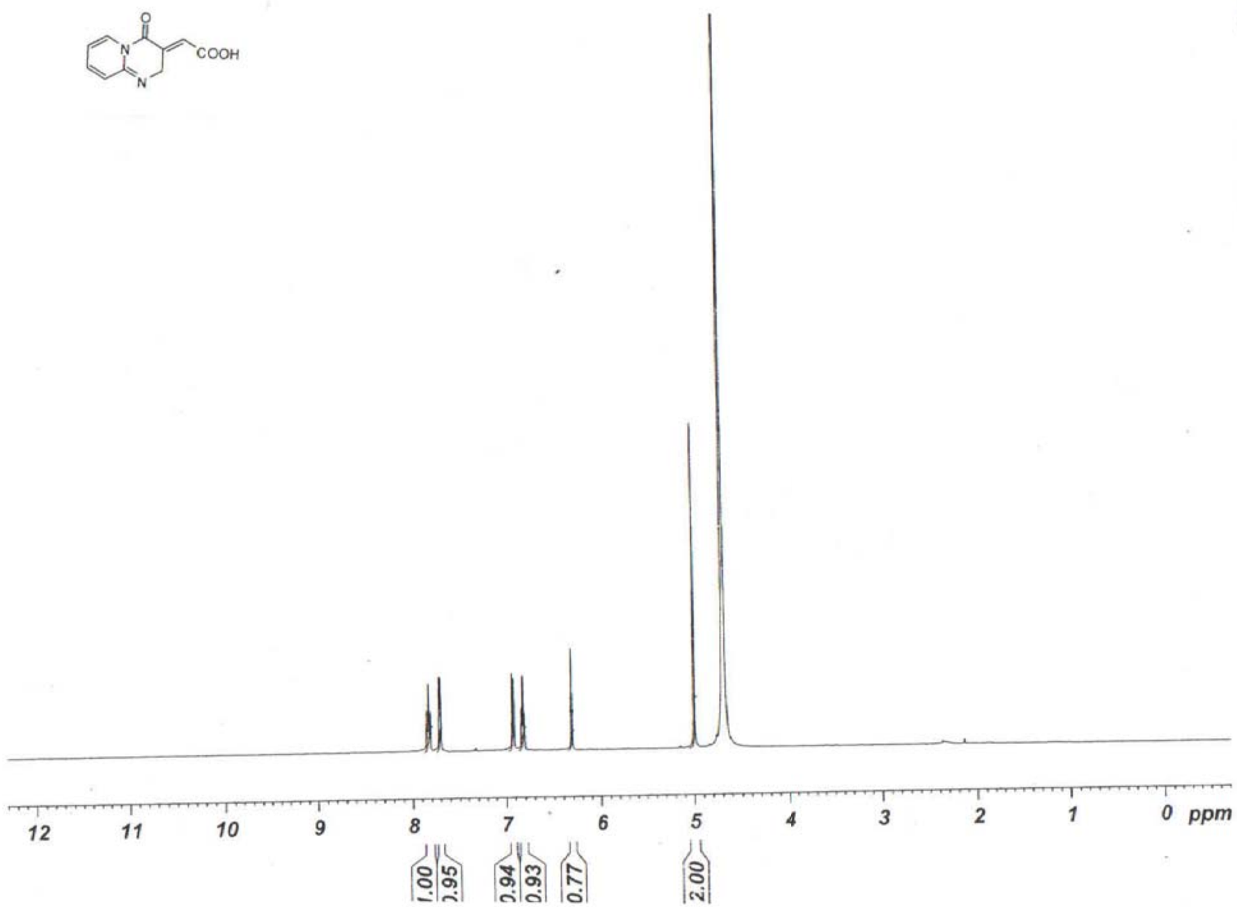
^{1}H Shift in ppm	Hydrogen	Observed ^{13}C connectivities
6.3	H_3'	C_2, C_3, C_4, C_3''
5.00	H_4	C_2, C_3, C_3'
7.8	H_6	C_8, C_{10}
6.8	H_7	C_6, C_9
7.7	H_8	C_7, C_{10}
6.9	H_9	C_7, C_{10}

The formation of the 2-oxo isomer was confirmed by the C=O absorption at 1670 cm^{-1} in the IR spectrum which was the characteristic feature of 2-oxo isomer **(Liu et al, 1997).** Also, as expected, a strongly deshielded aromatic proton at the 6th position (δ 8-9) due to the anisotropy of the carbonyl group at the 4th position was not observed in the ^{1}H NMR spectrum **(Geraldine C 2008).** A long range $^3J_{CH}$ correlation between the H_6 and C_4 carbon was found to be absent in the HMBC spectrum again confirming the formation of 2-oxo isomer. The NMR data and the COSY and HMBC correlations for 7-methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid **209d** are given in **Tables 3, 4 and Figures – 9 -14.**

2AM-PY.................R

FIGURE -1

^{1}HNMR SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



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PROCNO                   1

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PULPROG               zg30
TD                   32768
SOLVENT                D2O
NS                      16
DS                       2
SWH            10330.578 Hz
FIDRES          0.315264 Hz
AQ             1.5860212 sec
RG                     203
DW                  48.400 usec
DE                    6.00 usec
TE                   297.4 K
D1            1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.65 usec
PL1                   0.00 dB
SFO1           500.1330885 MHz

F2 - Processing parameters
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SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
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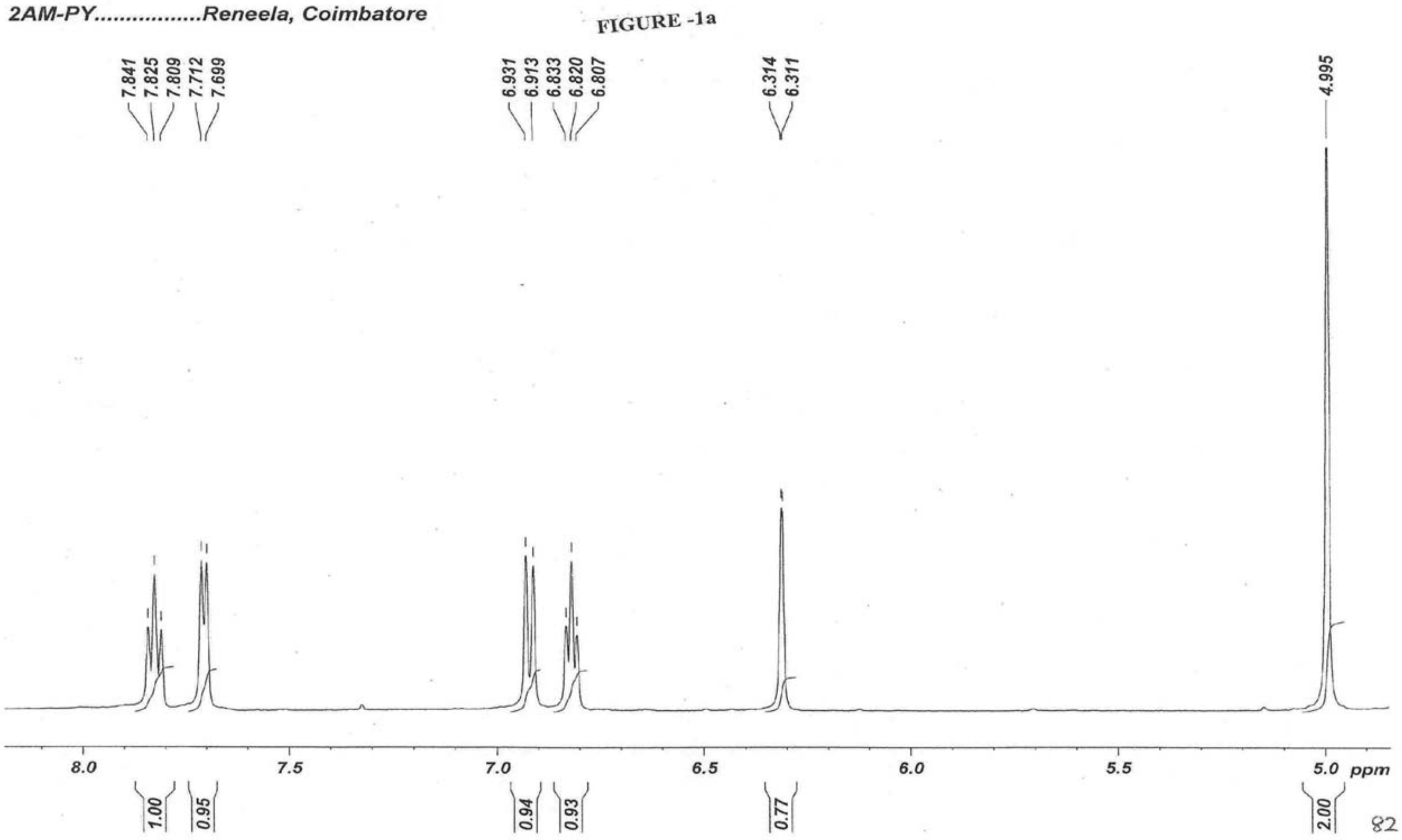
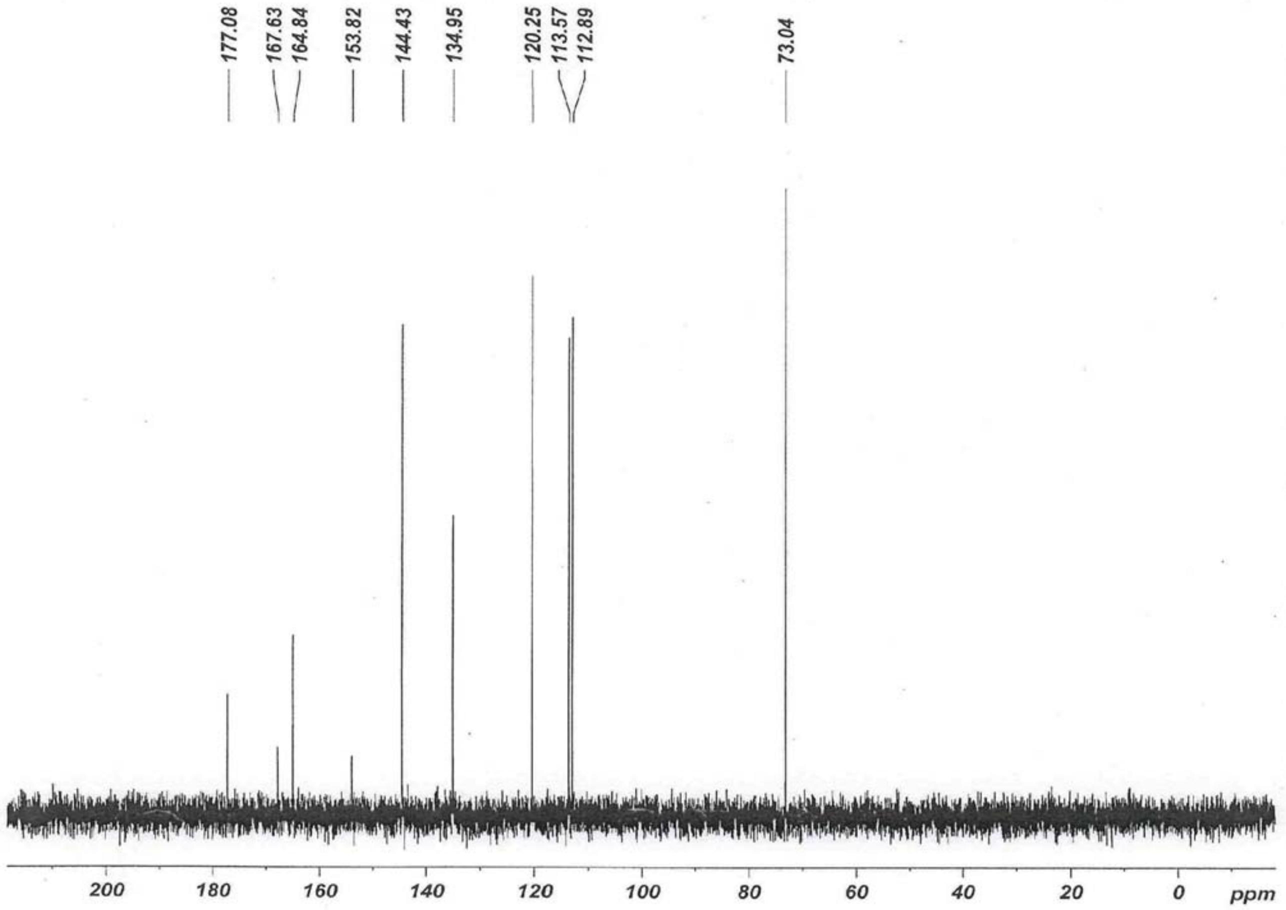

2AM-PY................Reneela, Coimbatore
7.841
7.825
7.809
7.712
7.699
6.931
6.913
6.833
6.820
6.807
6.314
6.311
4.995
8.0
7.5
7.0
6.5
6.0
5.5
5.0 ppm
1.00
0.95
0.94
0.93
0.77
2.00

FIGURE -1a

FIGURE -2

^{13}C NMR SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

2AM-PY.................Reneela



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TD                 32768
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DS                     4
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FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.00 usec
TE                 298.1 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

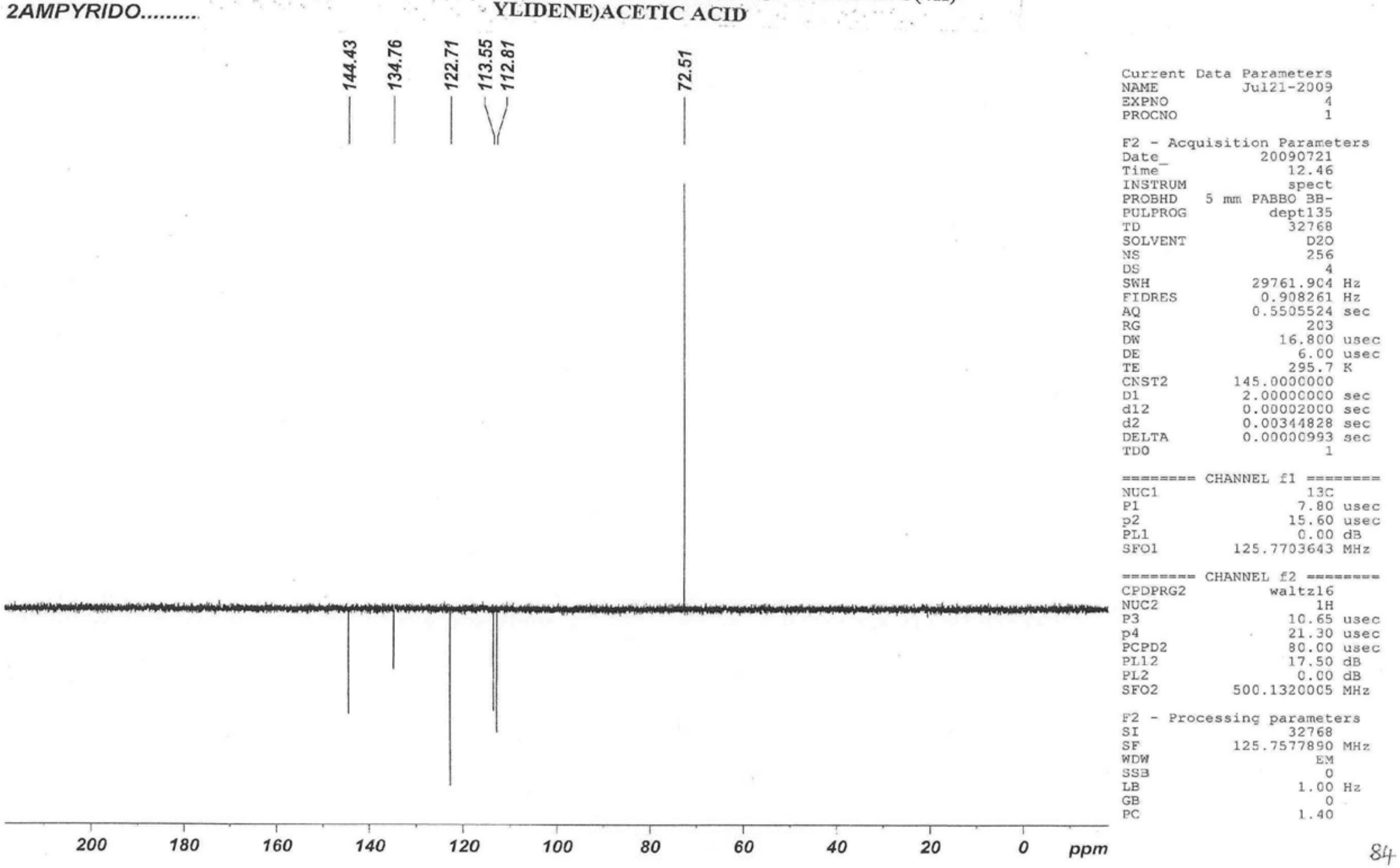
======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
PL1                 0.00 dB
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL12               17.50 dB
PL13               17.50 dB
PL2                 0.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

FIGURE -3

DEPT SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



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PROCNO                 1

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PULPROG          dept135
TD                 32768
SOLVENT              D2O
NS                   256
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.00 usec
TE                 295.7 K
CNST2        145.0000000
D1            2.00000000 sec
d12           0.00002000 sec
d2            0.00344828 sec
DELTA         0.00000993 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
p2                 15.60 usec
PL1                 0.00 dB
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
P3                 10.65 usec
p4                 21.30 usec
PCPD2              80.00 usec
PL12               17.50 dB
PL2                 0.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```
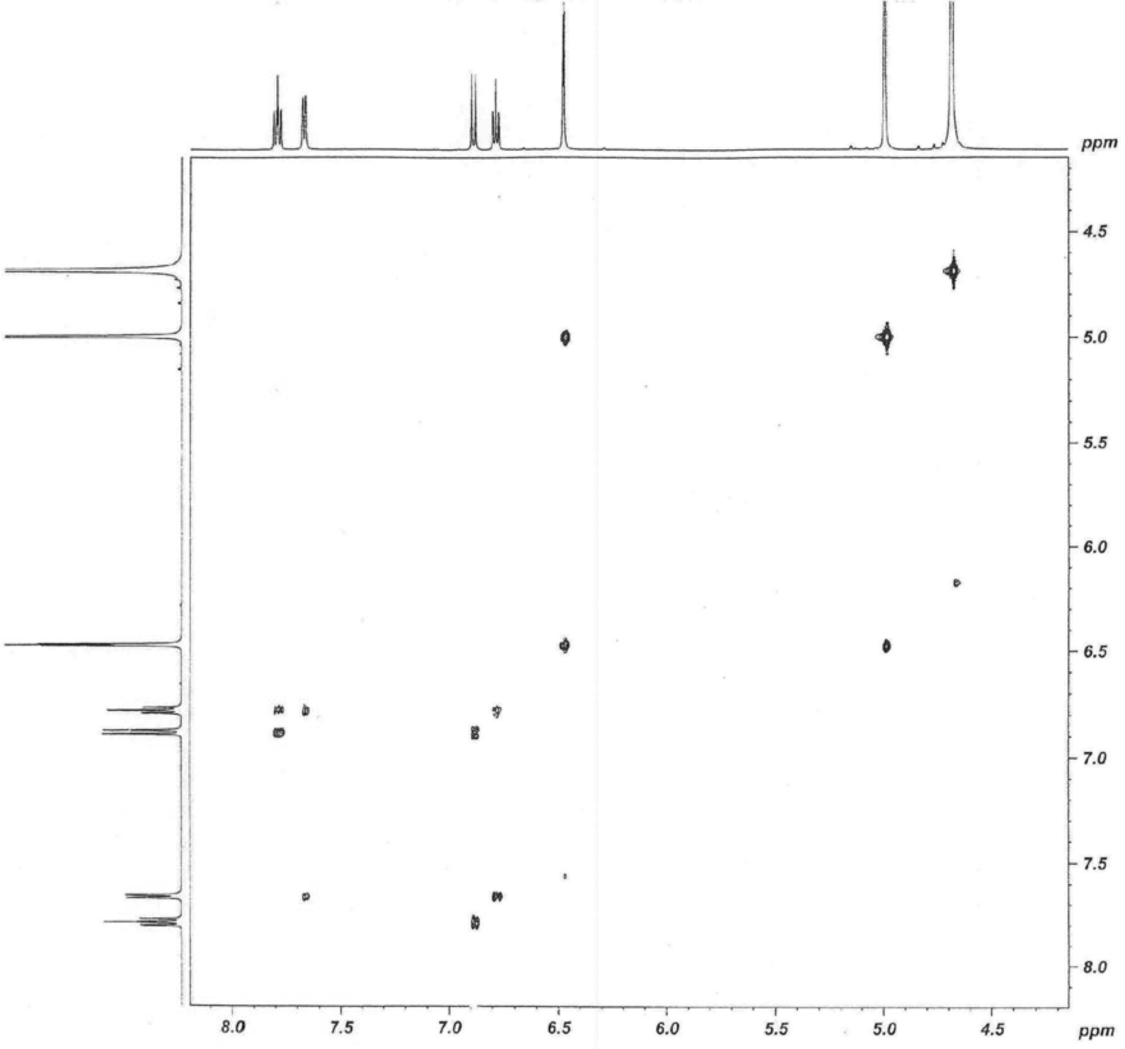

FIGURE -4

COSY SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

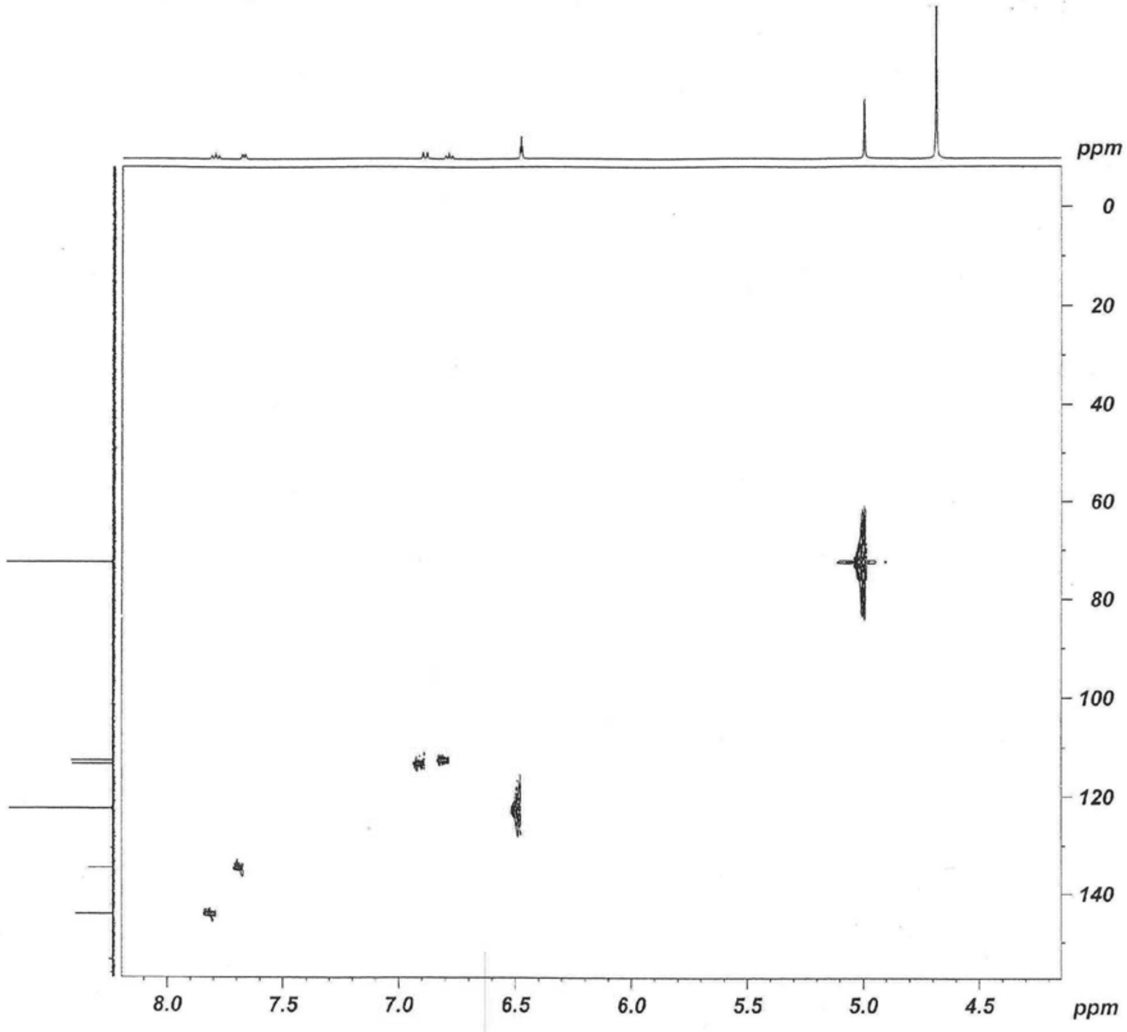


```
Current Data Parameters
NAME          Jul21-2009
EXPNO                 26
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090721
Time               18.04
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG         cosygpqf
TD                  2048
SOLVENT              D2O
NS                     1
DS                     8
SWH             2024.292 Hz
FIDRES          0.988424 Hz
AQ             0.5059060 sec
RG                    64
DW               247.000 usec
DE                  6.00 usec
TE                 296.4 K
d0            0.00000300 sec
D1            1.13422596 sec
d13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00049400 sec

======== CHANNEL f1 ========
NUC1                  1H
P0                 10.65 usec
P1                 10.65 usec
PL1                 0.00 dB
SFO1         500.1330863 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1               10.00 %
GPZ2               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
ND0                    1
TD                   128
SFO1            500.1331 MHz
FIDRES         15.814777 Hz
SW                 4.048 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300000 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300000 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
```

FIGURE -5

2AM-Pyrido........

HETCOR SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

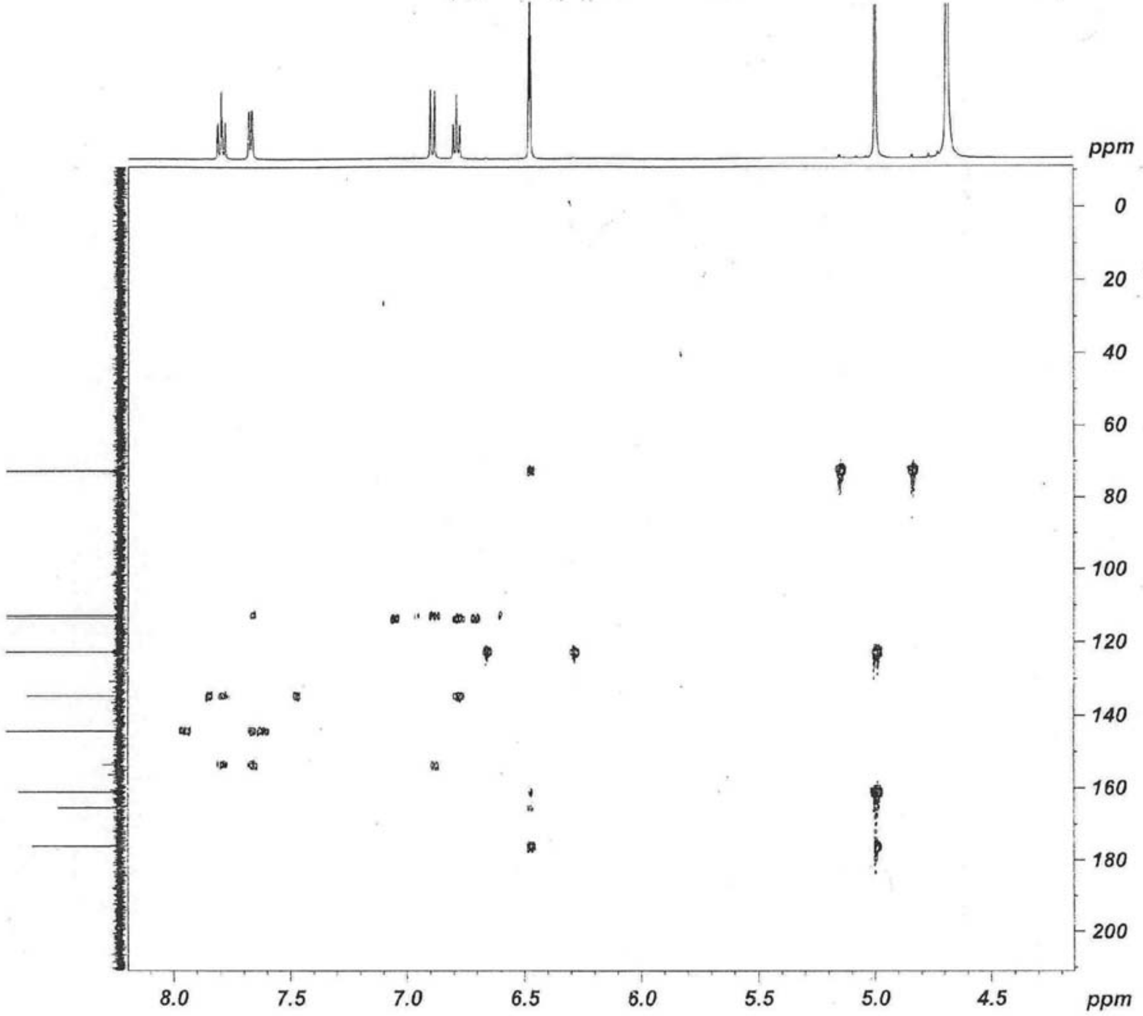


```
Current Data Parameters
NAME             Jul21-2009
EXPNO                    29
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090721
Time                  19.06
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG            hsqcetgp
TD                     1024
SOLVENT                 D2O
NS                        2
DS                       16
SWH                2024.292 Hz
FIDRES             1.976847 Hz
AQ                0.2529780 sec
RG                      203
DW                  247.000 usec
DE                     6.00 usec
TE                    296.8 K
CNST2           145.0000000
d0               0.00000300 sec
D1               1.32366705 sec
d11              0.03000000 sec
d13              0.00000400 sec
D16              0.00020000 sec
d4               0.00172414 sec
DELTA            0.00122730 sec
DELTA1           0.00071614 sec
IN0              0.00002400 sec
ST1CNT                  128
ZGOPTNS

======== CHANNEL f1 ========
NUC1                     1H
P1                    10.65 usec
p2                    21.30 usec
P28                    0.00 usec
PL1                    0.00 dB
SFO1            500.1330863 MHz

======== CHANNEL f2 ========
CPDPRG2                garp
NUC2                    13C
P3                     7.80 usec
p4                    15.60 usec
PCPD2                 65.00 usec
PL12                  18.00 dB
PL2                    0.00 dB
SFO2            125.7671682 MHz

====== GRADIENT CHANNEL =====
GPNAM1             SINE.100
GPNAM2             SINE.100
GPZ1                  80.00 %
GPZ2                  20.10 %
P16                 1000.00 usec

F1 - Acquisition parameters
ND0                       2
TD                      256
SFO1               125.7672 MHz
FIDRES            81.380211 Hz
SW                  165.650 ppm
FnMODE        Echo-Antiecho

F2 - Processing parameters
SI                     1024
SF              500.1300000 MHz
WDW                   QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2          echo-antiecho
SF              125.7577890 MHz
WDW                   QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
```

FIGURE -6

2AM-Pyrido......

HMBC SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



```
Current Data Parameters
NAME          Jul21-2009
EXPNO                 28
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090721
Time               18.33
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG       hmbcgpndqf
TD                  4096
SOLVENT              D2C
NS                     8
DS                    16
SWH             2024.292 Hz
FIDRES          0.494212 Hz
AQ             1.0117620 sec
RG                   203
DW               247.000 usec
DE                  6.00 usec
TE                 297.1 K
CNST13         8.0000000
d0            0.00000300 sec
D1            0.79548788 sec
D16           0.00020000 sec
d6            0.06250000 sec
IN0           0.00001790 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
p2                 21.30 usec
PL1                 0.00 dB
SFO1         500.1330363 MHz

======== CHANNEL f2 ========
NUC2                 13C
P3                  7.80 usec
PL2                 0.00 dB
SFO2         125.7703443 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPNAM3          SINE.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
ND0                    2
TD                   128
SFO1            125.7703 MHz
FIDRES        218.226257 Hz
SW               222.095 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300000 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577890 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
```

FIGURE –7

COSY- CORRELATIONS OBSERVED IN 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

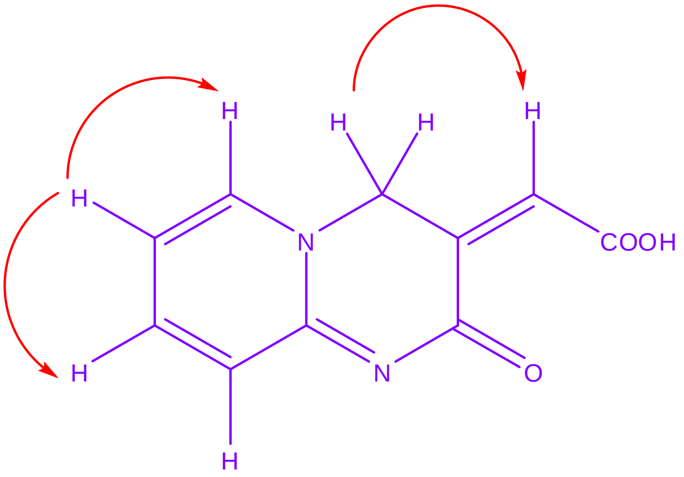


FIGURE – 8

HMBC- ORRELATIONS OBSERVED IN 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

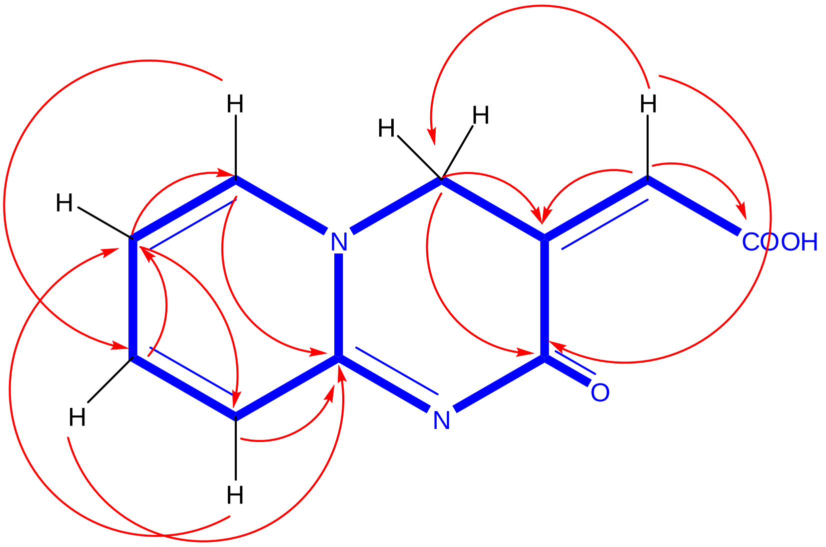


TABLE -3

NMR DATA OF 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Multip-licity/no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	Dept -135	C^{13} shift in ppm	Carbon	Dept-135
6.47	t/1	H_3'	176	C_2	-C	123	C_7	-C
5.00	d/2	H_4	161	C_3	-C	16	C_7-Me	$-CH_3$
7.6	d(d)/1	H_6	122	C_3'	-CH	132	C_8	CH
2.10	s/3	H_7- Me	165	C_3''	-C	113	C_9	CH
7.4	t/1	H_8	72	C_4	$-CH_2$	152	C_{10}	-C
6.8	d/1	H_9	146	C_6	-CH			

TABLE –4

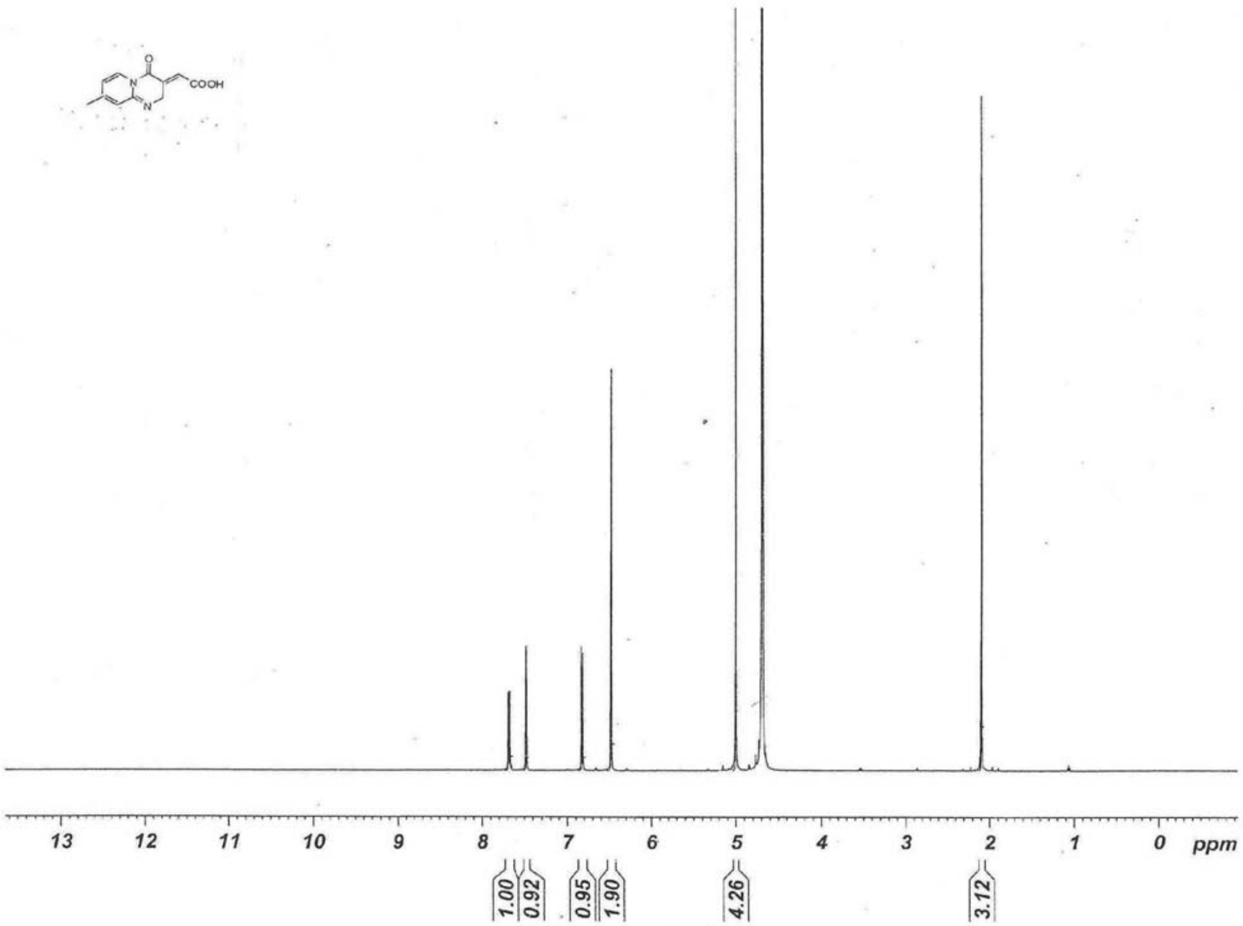
HMBC CORRELATIONS OBSERVED IN 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Hydrogen	Observed ^{13}C connectivities
6.47	H_3'	C_2,C_3,C_4, C_3''
5.00	H_4	C_2,C_3, C_3'
7.6	H_6	C_8,C_{10}
2.10	-	-
7.4	H_8	C_7,C_{10}
6.8	H_9	C_7,C_{10}

FIGURE - 9

5ME-PY........

^{1}HNMR SPECTRUM OF7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



```
Current Data Parameters
NAME          Jun23-2009
EXPNO                  9
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090623
Time               16.42
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 32768
SOLVENT              D2O
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ            1.5860212 sec
RG                   203
DW                48.400 usec
DE                  6.00 usec
TE                 296.5 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
PL1                 0.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

9D

5ME-PY..................Reneela, Coimbatore

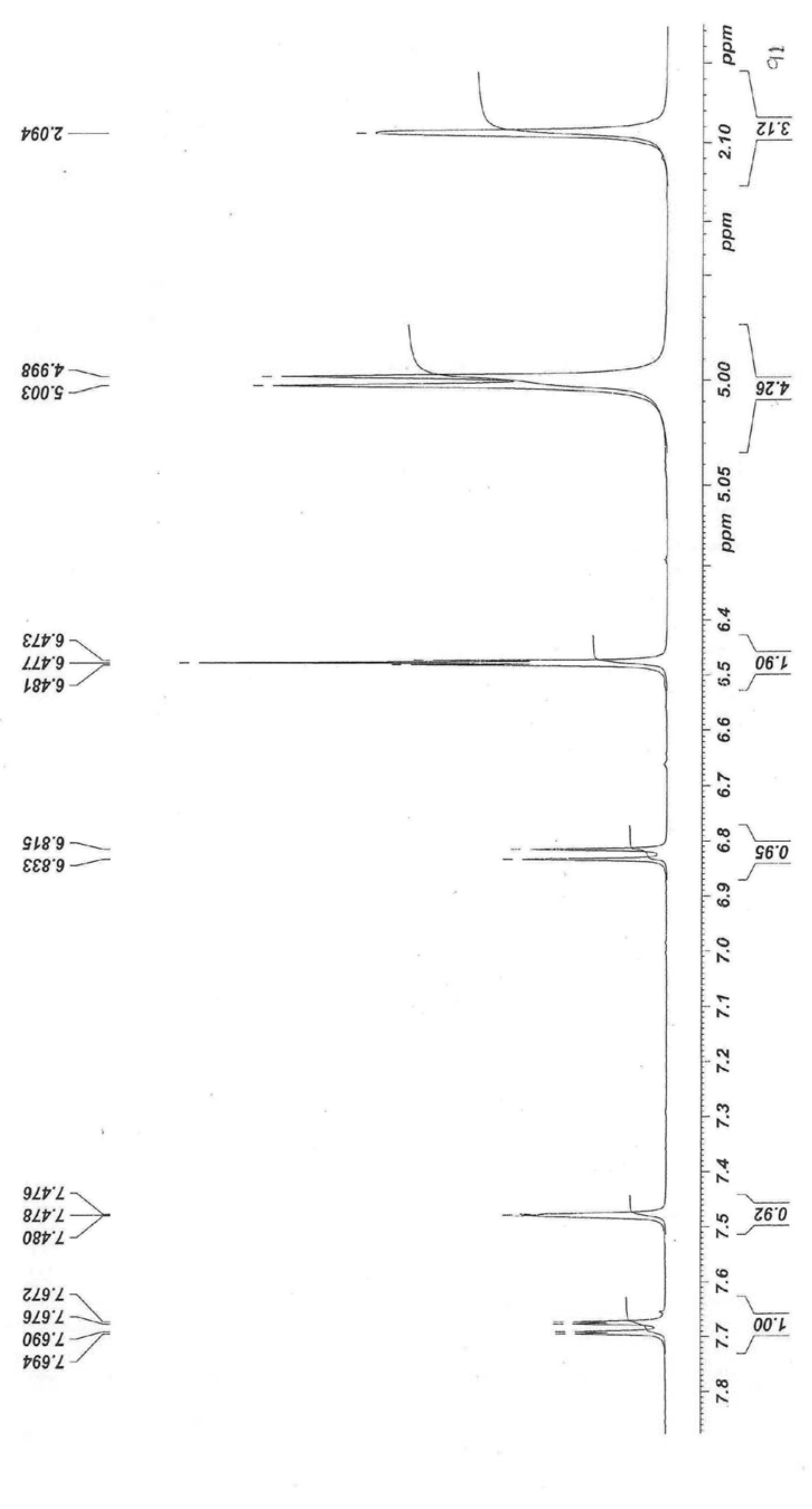
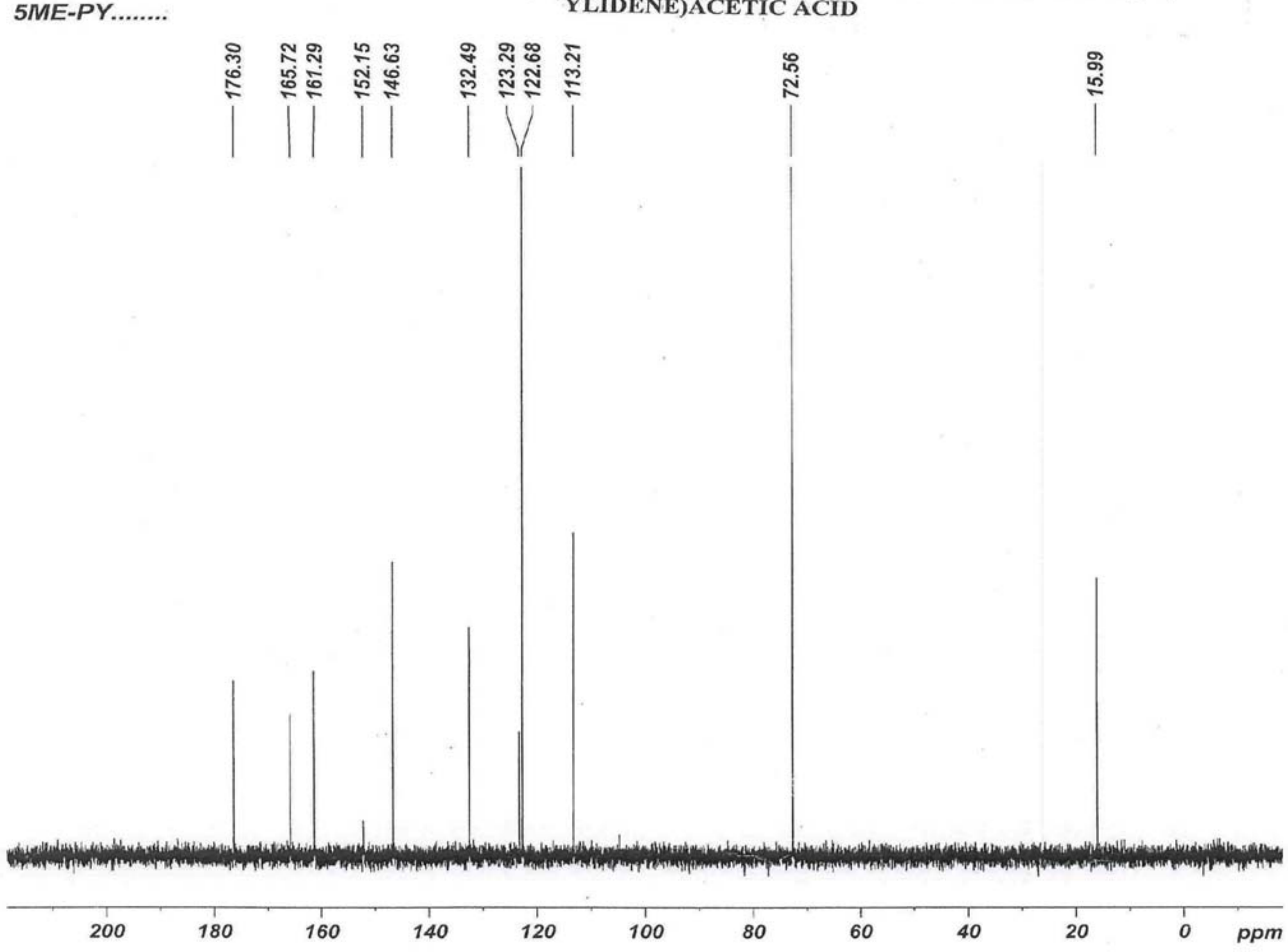


FIGURE - 9a

FIGURE - 10

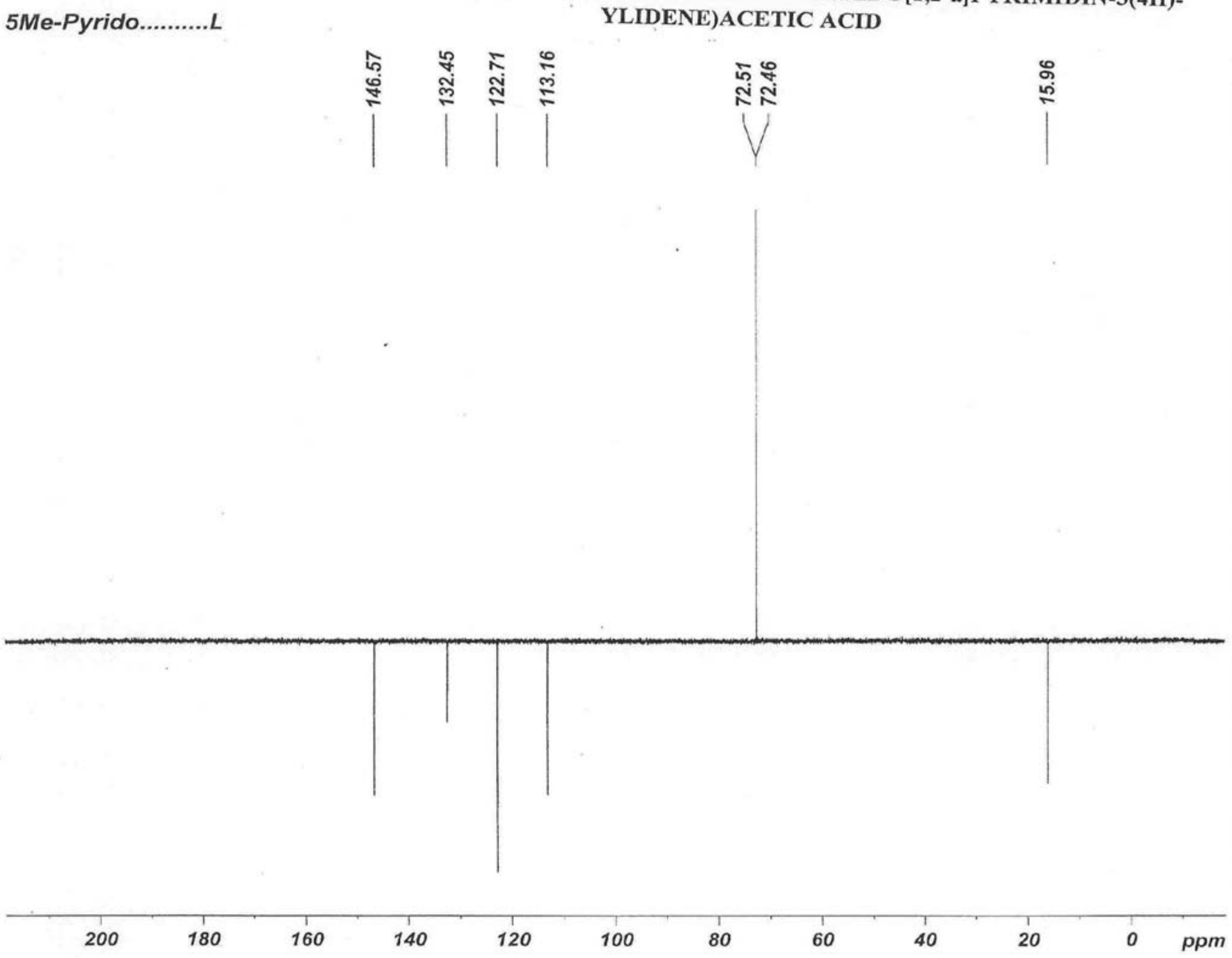
^{13}CNMR SPECTRUM OF7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



```
Current Data Parameters
NAME             Jun23-2009
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090623
Time                  15.46
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                    32768
SOLVENT                 D2O
NS                     1024
DS                        4
SWH              29761.904 Hz
FIDRES            0.908261 Hz
AQ               0.5505524 sec
RG                      203
DW                   16.800 usec
DE                     6.00 usec
TE                    298.1 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     7.80 usec
PL1                    0.00 dB
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL12                  17.50 dB
PL13                  17.50 dB
PL2                    0.00 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                    32768
SF             125.7577890 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

FIGURE -11

DEPT SPECTRUM OF7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



```
Current Data Parameters
NAME          Jul21-2009
EXPNO                 23
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090721
Time               17.49
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          dept135
TD                 32768
SOLVENT              D2O
NS                   256
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.00 usec
TE                 296.7 K
CNST2        145.0000000
D1            2.00000000 sec
d12           0.00002000 sec
d2            0.00344828 sec
DELTA         0.00000993 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
p2                 15.60 usec
PL1                 0.00 dB
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
P3                 10.65 usec
p4                 21.30 usec
PCPD2              80.00 usec
PL12               17.50 dB
PL2                 0.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

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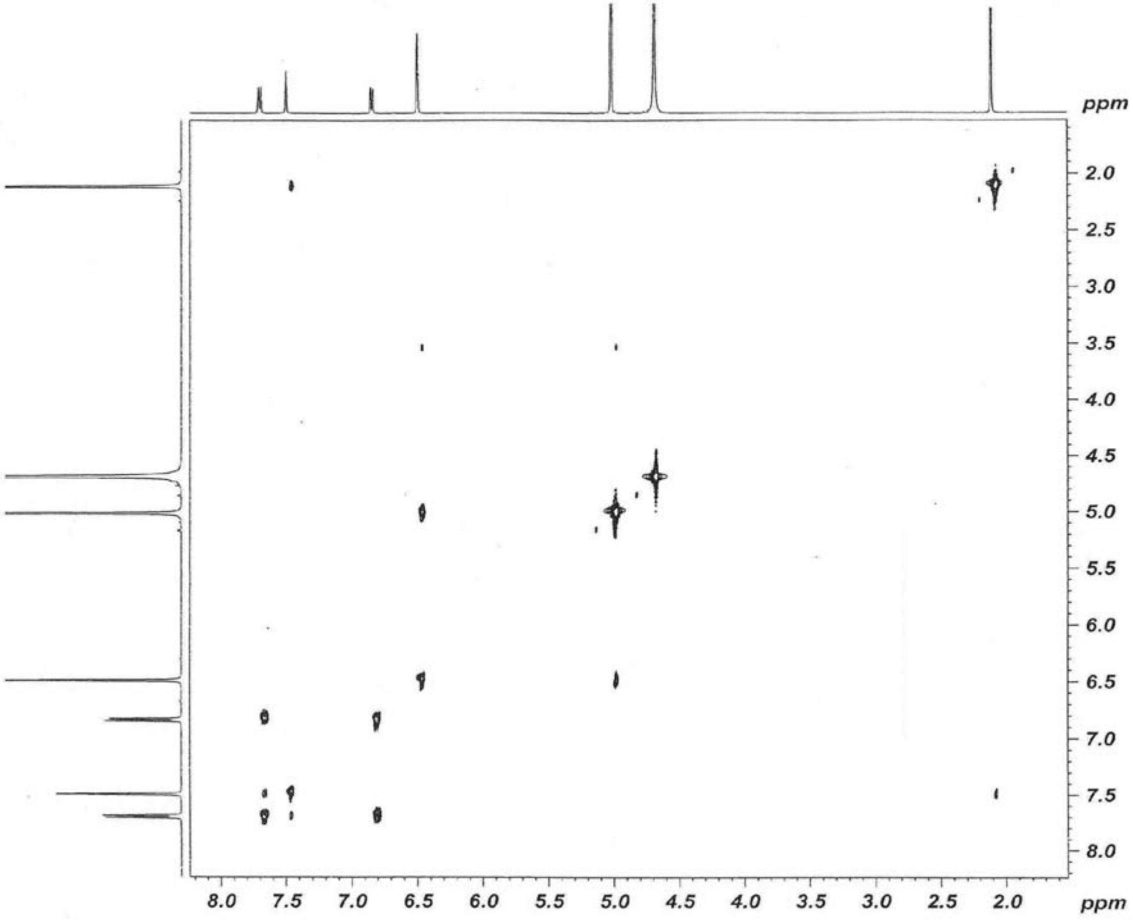
5Me-Pyrido.......

FIGURE -12

COSY SPECTRUM OF7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

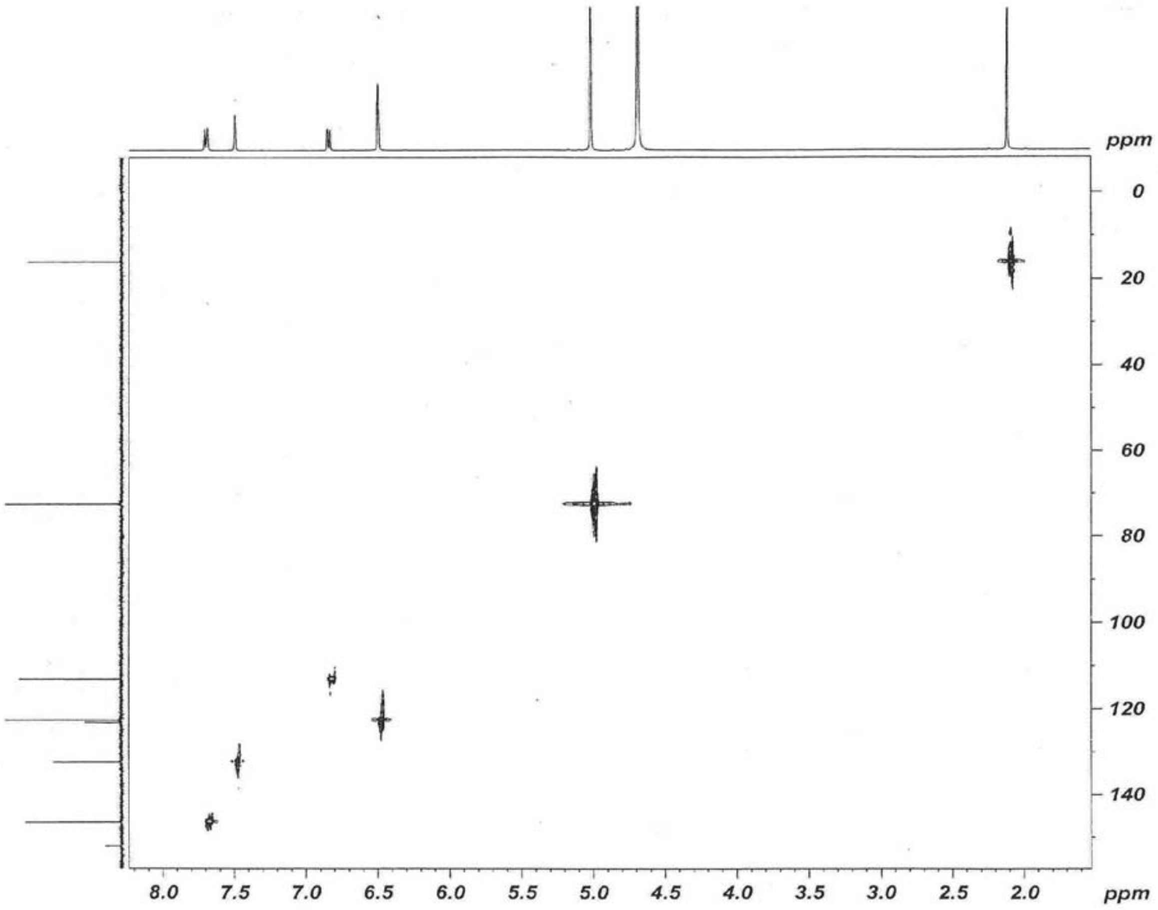


```
Current Data Parameters
NAME             Jul21-2009
EXPNO                    32
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090721
Time                  19.47
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG            cosygpqf
TD                     2048
SOLVENT                 D2O
NS                        1
DS                        8
SWH                3355.705 Hz
FIDRES             1.638528 Hz
AQ                0.3052020 sec
RG                       64
DW                  149.000 usec
DE                     6.00 usec
TE                    297.1 K
d0               0.00000300 sec
D1               1.33492994 sec
d13              0.00000400 sec
D16              0.00020000 sec
IN0              0.00029800 sec

======== CHANNEL f1 ========
NUC1                     1H
P0                    10.65 usec
P1                    10.65 usec
PL1                    0.00 dB
SFO1            500.1324422 MHz

====== GRADIENT CHANNEL =====
GPNAM1             SINE.100
GPNAM2             SINE.100
GPZ1                  10.00 %
GPZ2                  10.00 %
P16                 1000.00 usec

F1 - Acquisition parameters
ND0                       1
TD                      128
SFO1               500.1324 MHz
FIDRES            26.216442 Hz
SW                    6.710 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     1024
SF              500.1300000 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF              500.1300000 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
```

FIGURE - 13

5Me-Pyrido..........La

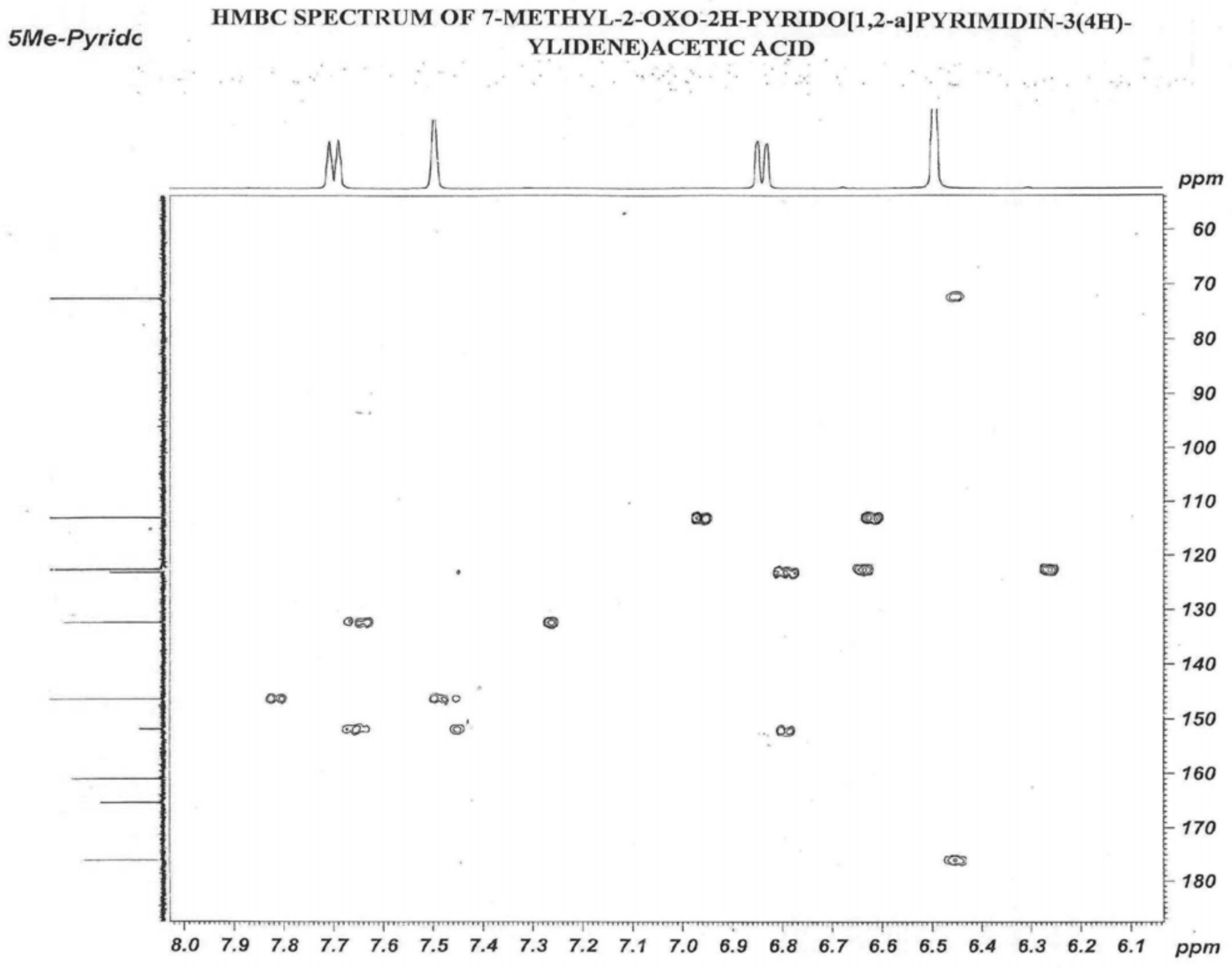
HETCOR SPECTRUM OF 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



```
Current Data Parameters
NAME          Jul21-2009
EXPNO                 33
PROCNO                 1

F2 - Acquisition Parameters
Date_           20090721
Time               19.52
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG         hsqcetgp
TD                  1024
SOLVENT              D2O
NS                     2
DS                    16
SWH             3355.705 Hz
FIDRES          3.277055 Hz
AQ             0.1526260 sec
RG                   203
DW               149.000 usec
DE                  6.00 usec
TE                 296.9 K
CNST2        145.0000000
d0            0.00000300 sec
D1            1.42401898 sec
d11           0.03000000 sec
d13           0.00000400 sec
D16           0.00020000 sec
d4            0.00172414 sec
DELTA         0.00122730 sec
DELTA1        0.00071614 sec
IN0           0.00002400 sec
ST1CNT               128
ZGOPTNS

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
p2                 21.30 usec
P28                 0.00 usec
PL1                 0.00 dB
SFO1         500.1324422 MHz

======== CHANNEL f2 ========
CPDPRG2             garp
NUC2                 13C
P3                  7.80 usec
p4                 15.60 usec
PCPD2              65.00 usec
PL12               18.00 dB
PL2                 0.00 dB
SFO2         125.7671682 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
ND0                    2
TD                   256
SFO1            125.7672 MHz
FIDRES         81.380211 Hz
SW               165.650 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300000 MHz
WDW                QSINE
SSB                    2
LB                  0.00 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2        echo-antiecho
SF           125.7577890 MHz
WDW                QSINE
SSB                    2
LB                  0.00 Hz
GB                     0
```

FIGURE - 14

HMBC SPECTRUM OF 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



```
Current Data Parameters
NAME             Jul21-2009
EXPNO                    34
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090721
Time                  20.08
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG          hmbcgpndqf
TD                     4096
SOLVENT                 D2O
NS                        8
DS                       16
SWH                3355.705 Hz
FIDRES             0.819264 Hz
AQ                0.6103540 sec
RG                      203
DW                  149.000 usec
DE                     6.00 usec
TE                    296.7 K
CNST13            8.0000000
d0               0.00000300 sec
D1               1.19689596 sec
D16              0.00020000 sec
d6               0.06250000 sec
IN0              0.00001790 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    10.65 usec
p2                    21.30 usec
PL1                    0.00 dB
SFO1            500.1324422 MHz

======== CHANNEL f2 ========
NUC2                    13C
P3                     7.80 usec
PL2                    0.00 dB
SFO2            125.7703443 MHz

====== GRADIENT CHANNEL =====
GPNAM1            SINE.100
GPNAM2            SINE.100
GPNAM3            SINE.100
GPZ1                 50.00 %
GPZ2                 30.00 %
GPZ3                 40.10 %
P16                1000.00 usec

F1 - Acquisition parameters
ND0                       2
TD                      128
SFO1               125.7703 MHz
FIDRES           218.226257 Hz
SW                  222.095 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     1024
SF              500.1300000 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF              125.7577890 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
```

FIGURE – 15

COSY- CORRELATIONS OBSERVED IN 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

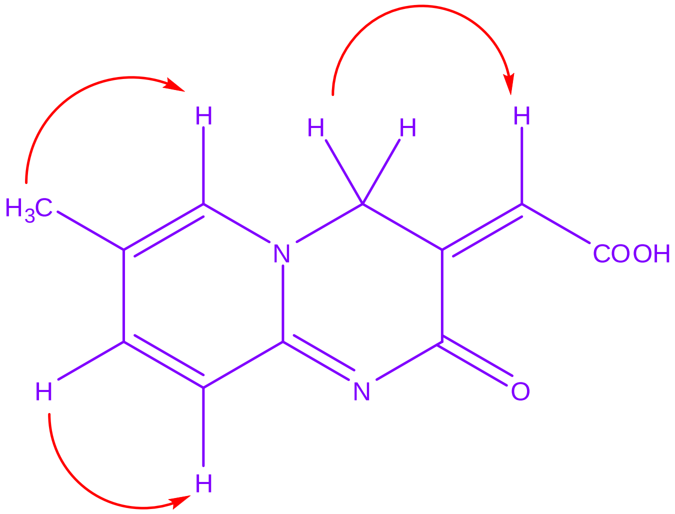
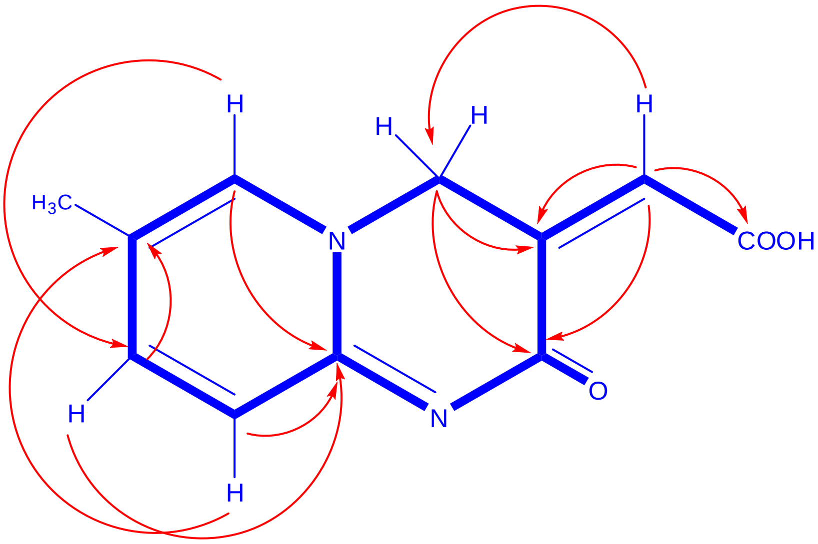


FIGURE – 16

HMBC CORRELATIONS OBSERVED IN 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID



A mechanistic rationalization of the product formed is given in Scheme -4, which involves the simultaneous condensation of amino group of pyridine nucleus with acid and cyclization by the nucleophilic attack of ring nitrogen to the carbon attached to the oxygen at ring junction. Under the similar condition 5-nitro-2-amino pyridine and 5-nitro-3-methyl-2-amino pyridine did not give the desired product with aconic acid, instead the starting compounds were recovered even under heating. This may be due to the strong electron withdrawing effect of nitro group which decreases the release of electron from the ring nitrogen. The yields of the products are summarized in **Table - 5.** The yield in the case of 3-methyl-2-amino pyridine was found to be high. This may be attributed to the electron donating methyl group which is in the ortho position to the amino group that enhances the nucleophilicity of both the nitrogen atoms.

SCHEME – 4

MECHANISM OF THE REACTION

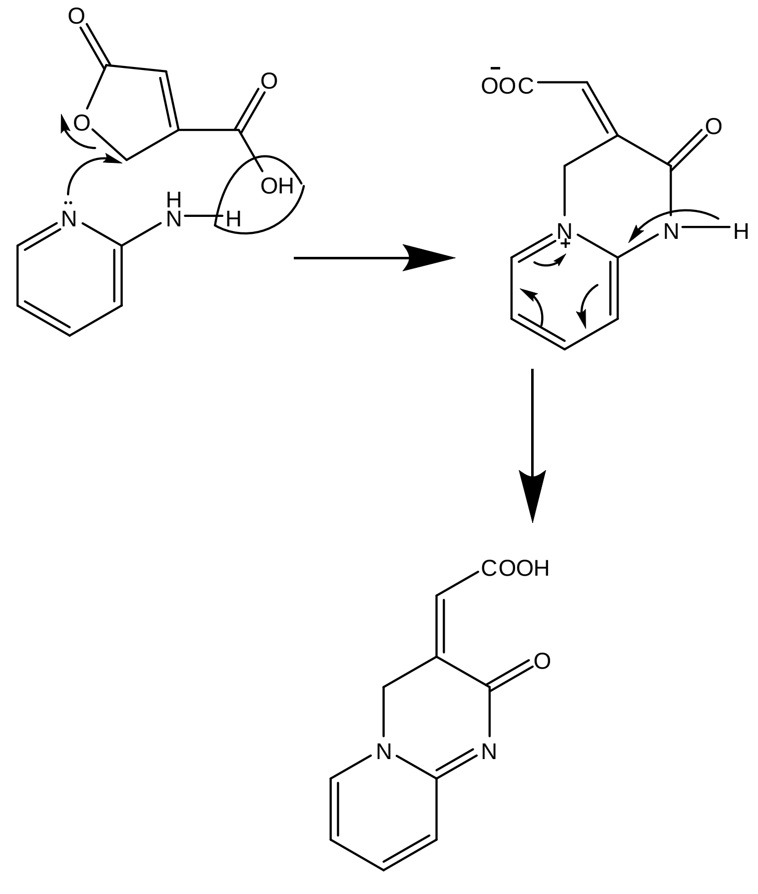


TABLE – 5

YIELD OF THE PRODUCTS FORMED

2-Amino pyridine	**R**	**Product (yield)**	**R**	**2-Amino pyridine**	**Product (yield)**
209a	H	91%	5-Br	209g	79%
209b	3-Me	96%	3-Me-5-Br	209h	76%
209c	4-Me	93%	4-Me-5-Br	209i	70%
209d	5-Me	88%	4,6-dimethyl-5-Br	209j	70%
209e	6-Me	82%	5-nitro	209k	no reaction
209f	4,6 Di-methyl	85%	3-methyl-5-nitro	209l	no reaction

Usually in the case of 6-substituted-2-aminopyridines, condensation with participation of the ring nitrogen atom does not occur due to steric hindrance **(Lappin G.R 1949).** But the reaction between 2-amino pyridine with aconic acid proceeded smoothly in this case, probably due to steric factor not playing a significant role in the reaction. It was also interesting to find that no naphthyridine derivative was obtained in this case. Observed NMR data for the compounds 209b, 209c, 209 e-i are summarized in **Tables 6-12**. In all the compounds, only a very little difference in the chemical shifts of all the protons was observed.

The proposed structure was confirmed by the mass spectrum analysis. Mass spectrum of compound 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid **Figure -17** registered M^+ peak at m/z - 204 and other significant peaks were observed at m/z-193(8%), m/z-186(11%), m/z-180(20%) m/z-159(4%), m/z-146(17%), m/z-118(22%), m/z-95(8%), m/z-88(45%), m/z-74(20%), and m/z-66 (34%). Possible mass fragmentation pattern of the compound 209a is given in **chart -1. Figure– 18** gives the mass spectrum of the compound **209c.Table-13** summarizes the mass spectral data for compounds.

TABLE -6

NMR DATA OF 9-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
6.3	t/1	H_3'	177	C_2	105	C_7
5.0	s/2	H_4	143	C_3	113	C_8
7.7	d(d)/1	H_6	122	C_3'	120	C_9
6.8	t/1	H_7	164	C_3''	15	C_9-Me
7.6	d(d)/1	H_8	73	C_4	153	C_{10}
2.1	s/3	H_9-Me	132	C_6		

TABLE -7

NMR DATA OF 8-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
6.3	t/1	H_3'	173	C_2	109	C_7
4.9	s/2	H_4	162	C_3	141	C_8
7.7	s/1	H_6	121	C_3'	20	C_8-Me
6.7	d(d)/1	H_7	164	C_3''	113	C_9
2.2	s/3	H_8-Me	71	C_4	157	C_{10}
6.8	s/1	H_9	151	C_6		

TABLE -8

NMR DATA OF 6-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	**Multiplicity /no. of ^{1}H**	**Hydrogen**	**C^{13} shift in ppm**	**Carbon**	**C^{13} shift in ppm**	**Carbon**
6.47	t/1	H_3'	175	C_2	19	C_6-Me
5.0	d/2	H_4	162	C_3	111	C_7
2.3	s/3	H_6-Me	123	C_3'	112	C_8
6.6	d/2	H_7 & H_9	165	C_3''	145	C_9
7.5	q/1	H_8	73	C_4	156	C_{10}
			148	C_6		

TABLE -9

NMR DATA OF 6,8-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	**Multiplicity /no. of ^{1}H**	**Hydrogen**	**C^{13} shift in ppm**	**Carbon**	**C^{13} shift in ppm**	**Carbon**
6.3	t/1	H_3'	177	C_2	23	C_6 -Me
5.0	d/3	H_4	152	C_3	110.2	C_7
2.4	s/3	H_6-Me		C_3'	110.5	C_8
6.6	s/2	H_9 & H_7	163	C_3''	19	C_8 -Me
2.3	s/3	H_8-Me	73	C_4	121	C_9
			145	C_6	157	C_{10}

TABLE -10

NMR DATA OF 7-BROMO-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
6.5	t/2	$H_3{}'$	176	C_2	105	C_7
5.0	d/2	H_4	160	C_3	115	C_8
7.9	m/1	H_6 & H_7	165	$C_3{}''$	123	C_9 & $C_3{}'$
6.8	d/1	H_8	72	C_4	146	C_{10}
			135	C_6		

TABLE -11

NMR DATA OF 7-BROMO-9-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
6.4	t/1	$H_3{}'$	176	C_2	105	C_7
5.0	d/2	H_4	162	C_3	124	C_8
7.82	s/1	H_6	122	$C_3{}'$	145	C_9
7.80	s/1	H_8	166	$C_3{}''$	15	C_9-Me
2.1	s/3	H_9-Me	72	C_4	152	C_{10}
			132	C_6		

TABLE - 12

NMR DATA OF 7-BROMO-8-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
6.4	s/2	H_3'	176	C_2	109	C_7
5.0	d/2	H_4	162	C_3	22	C_8-Me
7.9	s/1	H_6	122	C_3'	113	C_9
2.3	s/3	H_8-Me	166	C_3''	157	C_{10}
6.8	s/1	H_9	72	C_4		
			135	C_6 & C_8		

TABLE -13

MASS SPECTRAL DATA OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACIDS

Compound	M$^+$(%) intensity	m/z (%) intensities
209b	219(2)	207(2), 189(2), 106(100), 96(33), 78(55), 69(2), 55.5(4)
209c	210(5)	207(88), 191(9), 165(9), 129(21), 119(32), 106(60), 91(61), 60(100), 57(63), 5(28)
209d	218(8)	204(8), 192(3), 186(8), 168(87), 161(9), 154(7), 154(5), 146(7), 136(9), 125(24), 118(6), 105(100), 96(80), 88(33), 77(42), 70(30)
209f	234(0.1)	197(100), 195(99), 170(19), 173(18), 126(7), 108(15), 97(72), 92(35), 80(10), 65(5.5)
209g	234(0.2)	220(1.2), 201(2), 185(4), 156(6), 146(1.2), 125(1.2), 120(100), 108(16), 97(39), 92(58), 78(8)
209j	312(22)	305(33), 295(17), 278(8), 120(100)

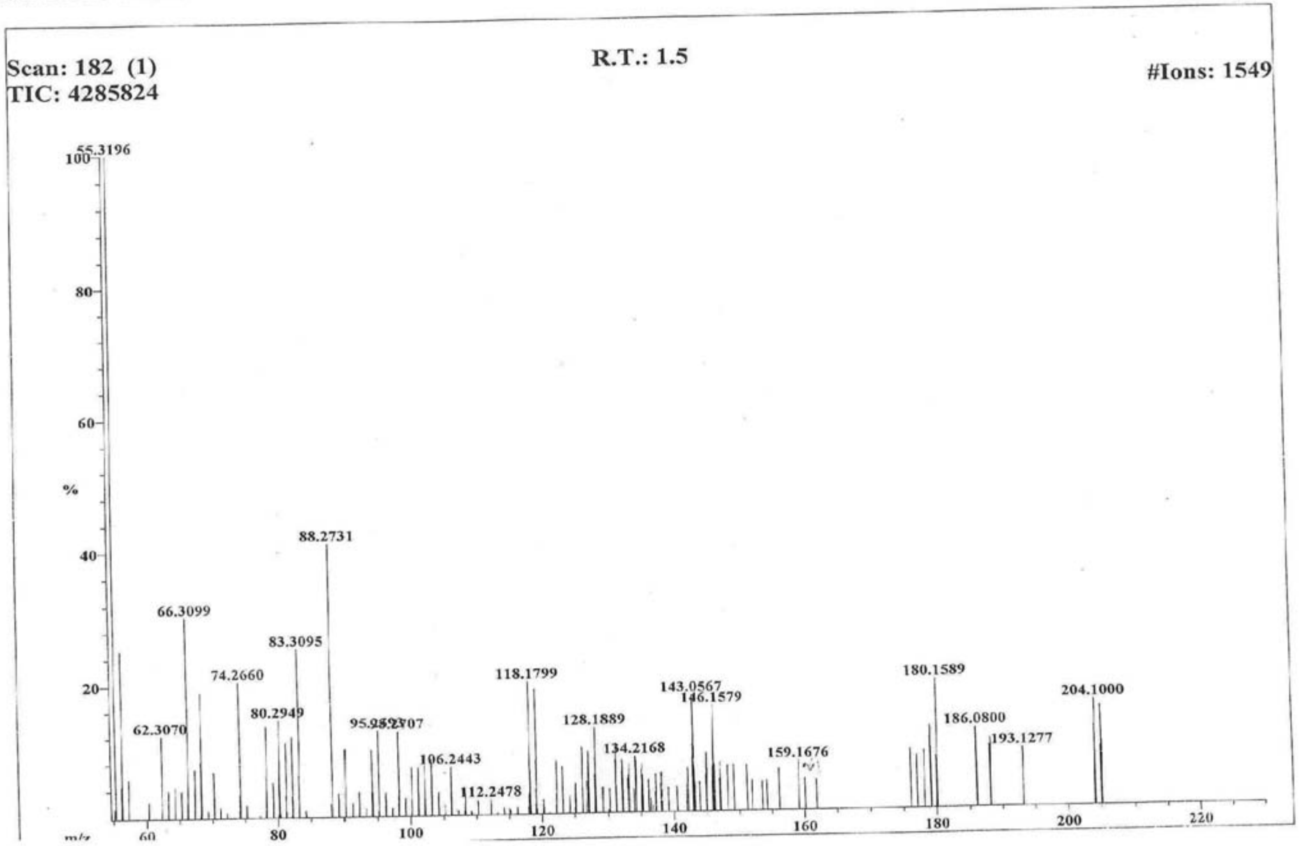
FIGURE 47

MASS SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

Date Run: 07-22-2009 (Time Run: 14:53:27)

File: 2AM-PY
Sample:
Instrument: JEOL GCmate
Inlet: Direct Probe

Ionization mode: EI+


Scan: 182 (1)
TIC: 4285824
R.T.: 1.5
#Ions: 1549

104

Page 1

FIGURE -18

MASS SPECTRUM OF 7-METHYL-2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

File: 5 Me
Sample:
Instrument: JEOL GCmate
Inlet: Direct Probe

Ionization mode: EI+

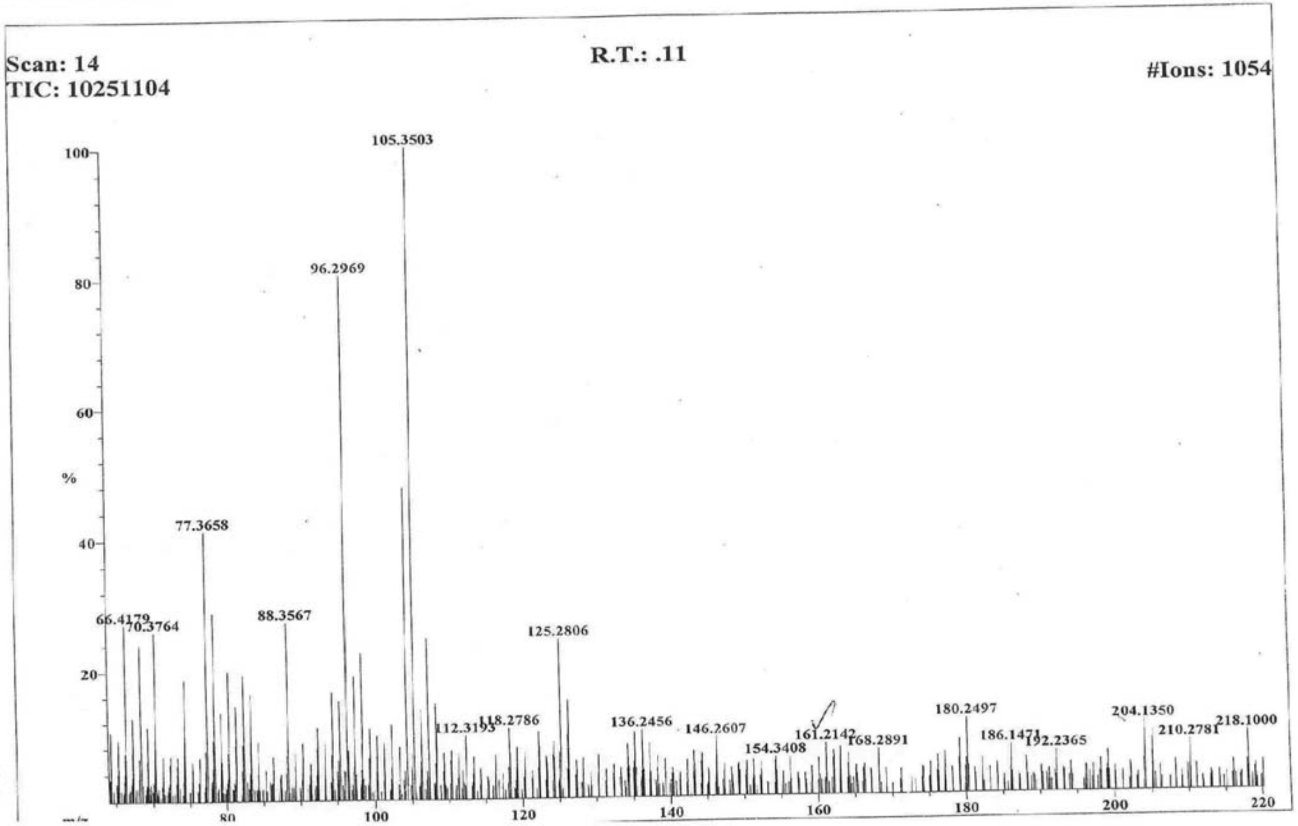
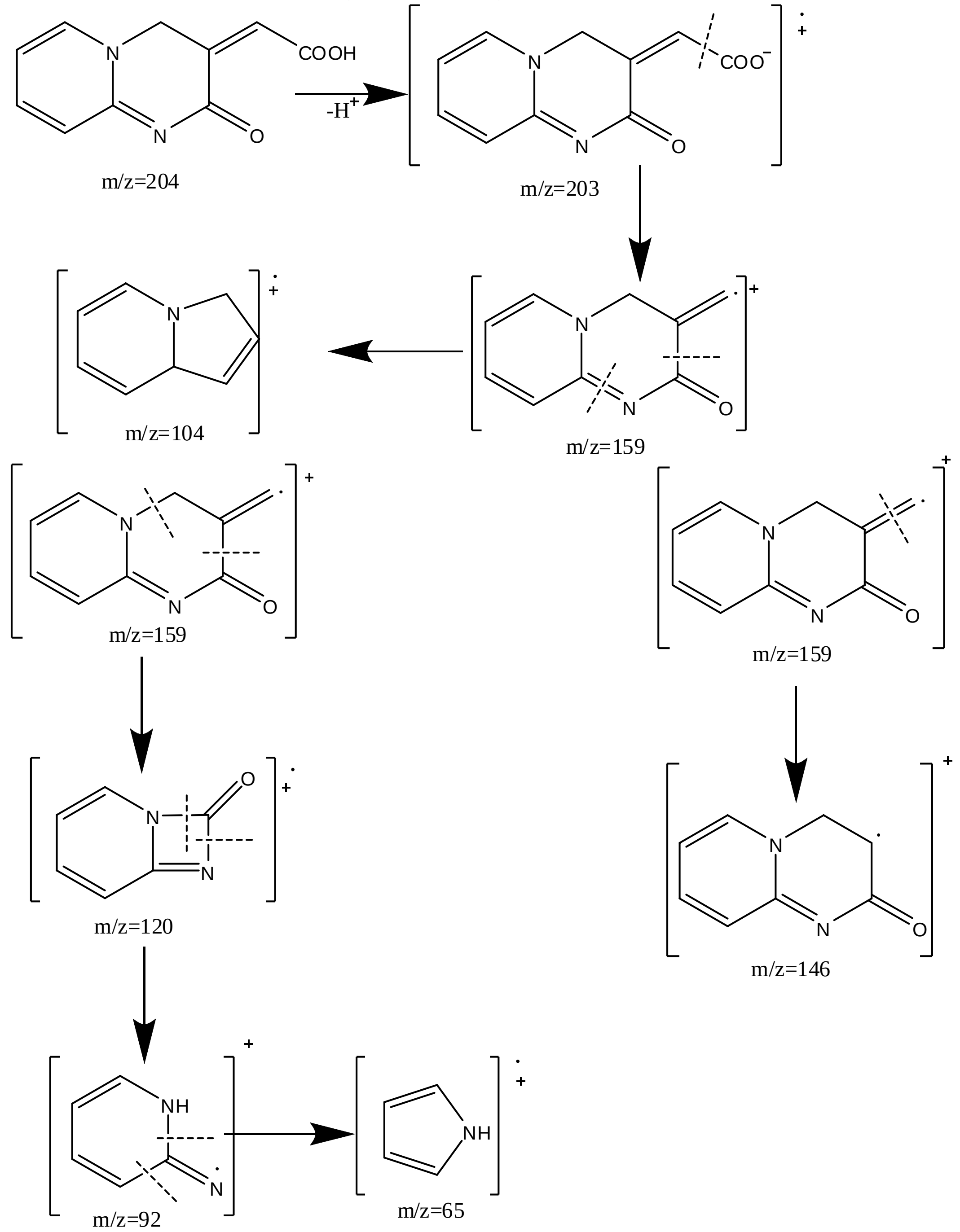


CHART - 1

MASS FRAGMENTATION PATTERN OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

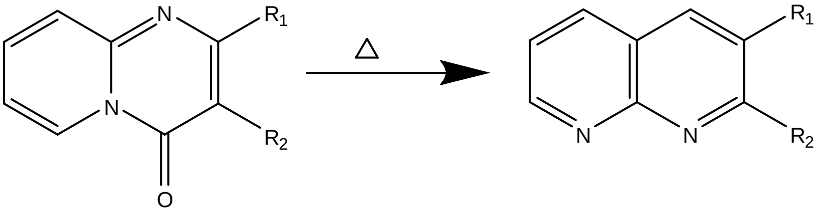


A difference in the suggested synthetic route, compared with other described methods of five membered synthons, is that the formation of the heterocyclic ring occurs in one step without any catalyst. Also neither heavy metals nor hazardous solvents were involved.

4.2 STUDY OF RING TRANSFORMATION OF PYRIDO[1,2-a] PYRIMIDINE YLIDENE ACETIC ACID

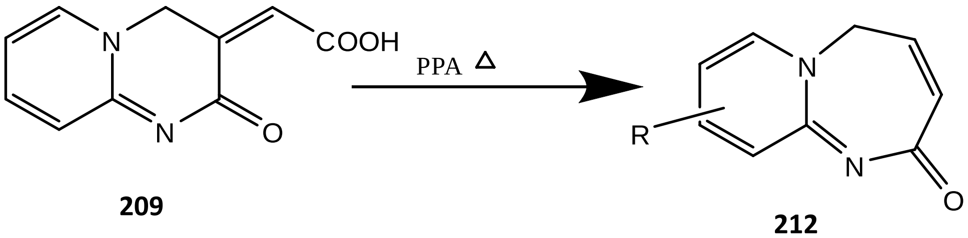
4.2.1 REACTION WITH PPA

Unsaturated bi- and polycyclic nitrogen bridge head ring systems containing a carbonyl group and substituent in the peri positions **210** undergo ring transformation under heating in high boiling solvents, Dowtherm A **(Meszaross 1975 and Istvin Hermecz et al, 1992)** and Marlotherm **(Kraemer W 1975)** to give condensed ring systems **211**. This type of ring transformation is involved in the synthesis of nalidixic acid and related antibacterial agents starting from a-azaamino methyl malonates.



210 **211**

Hence, an attempt was made to transform 2-oxo-2H-pyrido[1,2-a] pyrimidin-ylidene acetic acid into 1,8 naphthyridine derivatives. For this purpose 2-oxo-2H-pyrido[1,2-a] pyrimidin-ylidene acetic acid was refluxed with PPA in a steam bath. After workup and crystallization with pet ether, white needles were obtained. The compound formed was characterized by spectral means. Contrary to the expectation, the reaction underwent a thermal rearrangement yielding pyrido diazepines.



209 **212**

Scheme -5

R = H, 3-methyl, 4-methyl, 5-methyl, 6-methyl

A comparison of the IR spectrum of the compound **212** with that of starting material **209** showed the disappearance of the absorption due to carboxylic acid moiety. The absorptions at 3421 cm^{-1}, 1652 cm^{-1} and 1583cm^{-1}, were attributed to the C-H aromatic, C=O moiety and C=N of the pyrimidine ring respectively.

Evidence for the product formed comes from the fact that ^{1}H NMR spectrum **Figure-19** exhibited peaks at δ 4.5, 6.2, 6.9, 7.2, 7.6, 8.2, 8.4. ^{13}C spectrum **Figure-20** displayed nine signals at δ 52, 113, 119, 128, 137, 144, 147, 151 and 170 respectively along with M^{+} peak at m/z 160 in the mass spectrum**.** These two facts clearly indicated that decarboxylation could have occurred during the reaction.

Following significant predictions were also made from the spectrum analysis of the product.

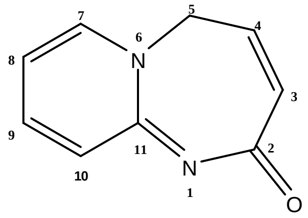
- The Dept – 135 spectrum **Figure-21** indicated the presence of six methine carbons and one methylene carbon. Hence the other two carbons must be quaternary carbons.
- The carbon signal at δ 167 disappeared which was originally for the -COOH carbon in the compound **209.**

A comparison of ^{1}H NMR spectrum of the product with that of the 2-oxo-2H-pyrido[1,2-a] pyrimidin-ylidene acetic acid **209** showed the presence of only two quaternary carbon atoms in the product instead of four. Also the number of methine carbon had increased from five to six. Hence it was concluded that among the four quaternary carbons present in the reactant, one carbon had left as CO_2 and the carbon at δ164 had been protonated. This had also been confirmed by the shift in the ^{13}C resonance of the sp^{3} hybridized carbon atom from δ 73 to δ 52 (a shift of 21 ppm) in the product due to the alpha effect observed with sp^{3} hybridized carbon atoms attached to the =CH in α position. Therefore it was concluded that a methine group had been attached to the methylene carbon resonating at δ 73 in the reactant **209.** Further the ^{1}H NMR spectrum exhibited a very characteristic splitting pattern (i.e) a doublet of triplet at δ 6.2 integrating for one proton indicting the presence of the CH_2-CH=CH-moiety. Hence a ring expansion could have occurred with the formation of a seven membered ring with the pyrido nucleus, which was identified as pyrido[1,2-a][1,3]diazepin-2(5H)-one **212**.

The structure of the compounds was also confirmed from 2D spectra **(Figures - 22-24)**. The following table summarizes the shift values for proton and carbon with their complete assignment for pyrido[1,2-a][1,3]diazepin-2(5H)-one **212a**.

TABLE- 14

NMR DATA OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



^1H Shift in ppm	Multiplicity /no. of ^1H	Hydrogen	C^{13} shift in ppm	Carbon	Dept-135
7.2	d(d)/1	H_3	170	C_2	-C
6.2	d(t)/1	H_4	144	C_3	-CH
4.6	t/2	H_5	128	C_4	-CH
8.3	d/1	H_7	52	C_5	$-CH_2$
7.7	d(d)/1	H_8	147	C_7	-CH
8.4	d(d)/1	H_9	138	C_8	-CH
6.9	m/1	H_{10}	119	C_9	-CH
			113	C_{10}	-CH
			151	C_{11}	

In the COSY spectrum, δ 4.6 showed cross peaks with δ 6.2 and δ 7.2. An analysis of the 2D HMBC spectrum revealed that the signal at δ 6.2 – H_4 showed cross peaks with the carbon signal at δ 144 – C_3 and δ 170 – C_2 confirming the proposed structure. The correlations seen in COSY and HMBC spectrum are given in **Figures - 25 and 26**. An interesting observation both from COSY and HMBC is that a long range ^{4}Jcoupling between H_7 and C_{10} was seen. Also ^{3}J coupling between H_8 and C_{11} was observed in the HMBC spectrum. The HMBC correlations are tabulated in **Table- 15.**

TABLE – 15

HMBC CORRELATIONS OBSERVED IN PYRIDO[1,2-a][1,3] DIAZEPIN-2(5H)-ONE

^{1}H Shift in ppm	Hydrogen	Observed ^{13}C connectivities
7.2	H_3	C_2, C_4
6.2	H_4	C_2, C_3
4.6	H_5	C_3, C_4
8.3	H_7	C_9, C_{10} & C_{11}
7.7	H_8	C_7, C_9 & C_{11}
8.4	H_9	C_{10}
6.9	H_{10}	C_7

The mass spectra of pyrido[1,2-a][1,3]diazepin-2(5H)-one is depicted in **Figure 27** and the possible mass fragmentation pattern is given in **Chart -2**. **Table – 16** summarizes the mass spectral data for pyrido[1,2-a][1,3]diazepin-2(5H)-one and 7-methyl pyrido[1,2-a][1,3] diazepin-2(5H)-one (**Figure-33)** .

TABLE - 16

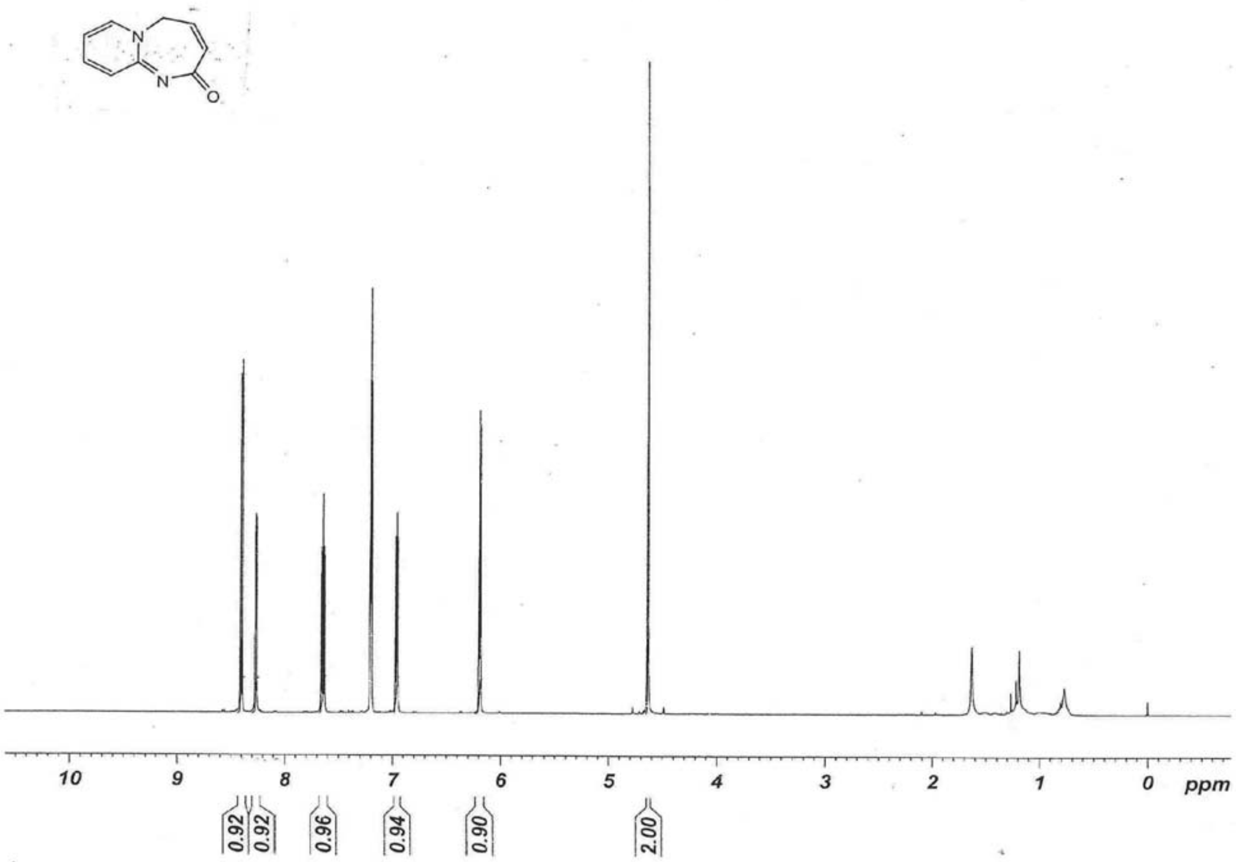
MASS SPECTRAL DATA OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE

Compound	M^+(%) intensity	m/z (%) intensities
212a	160(30)	133(4), 131(45), 119(10), 106(2), 104(100), 80(1), 78(90), 68(10), 66(10), 53(28)
212e	175(11)	174(68), 146(22), 145(100), 93(70), 66(21), 65(46), 64(10), 52(12)

FIGURE -19

^{1}HNMR SPECTRUM OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE

2AMPPA............Latha, CBE



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PROCNO                  1

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PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             10330.578 Hz
FIDRES           0.315264 Hz
AQ              1.5860212 sec
RG                    203
DW                 48.400 usec
DE                   6.00 usec
TE                  295.8 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.65 usec
PL1                  0.00 dB
SFO1          500.1330885 MHz

F2 - Processing parameters
SI                  32768
SF            500.1300390 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

2AMPPA...........Latha, CB

FIGURE - 19a

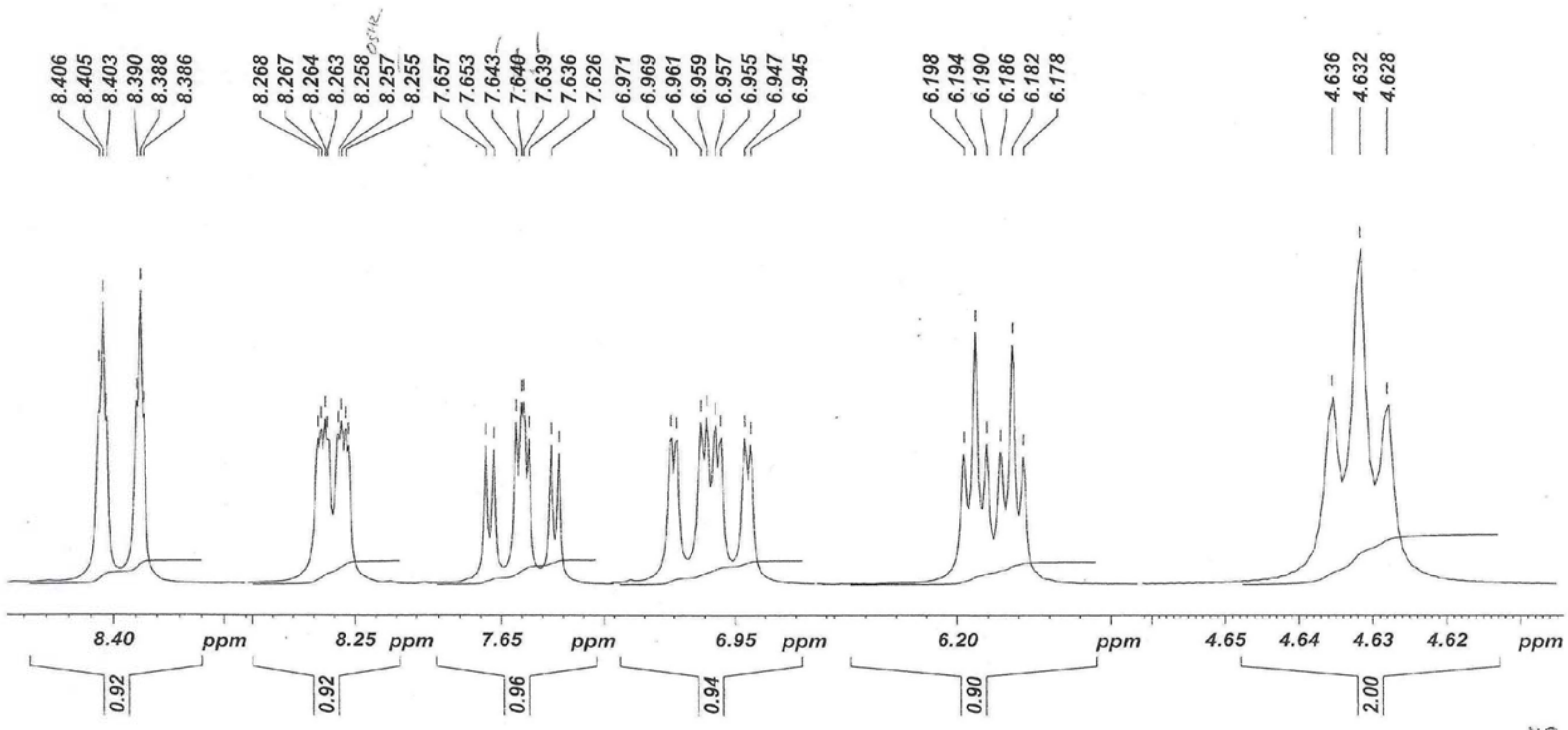
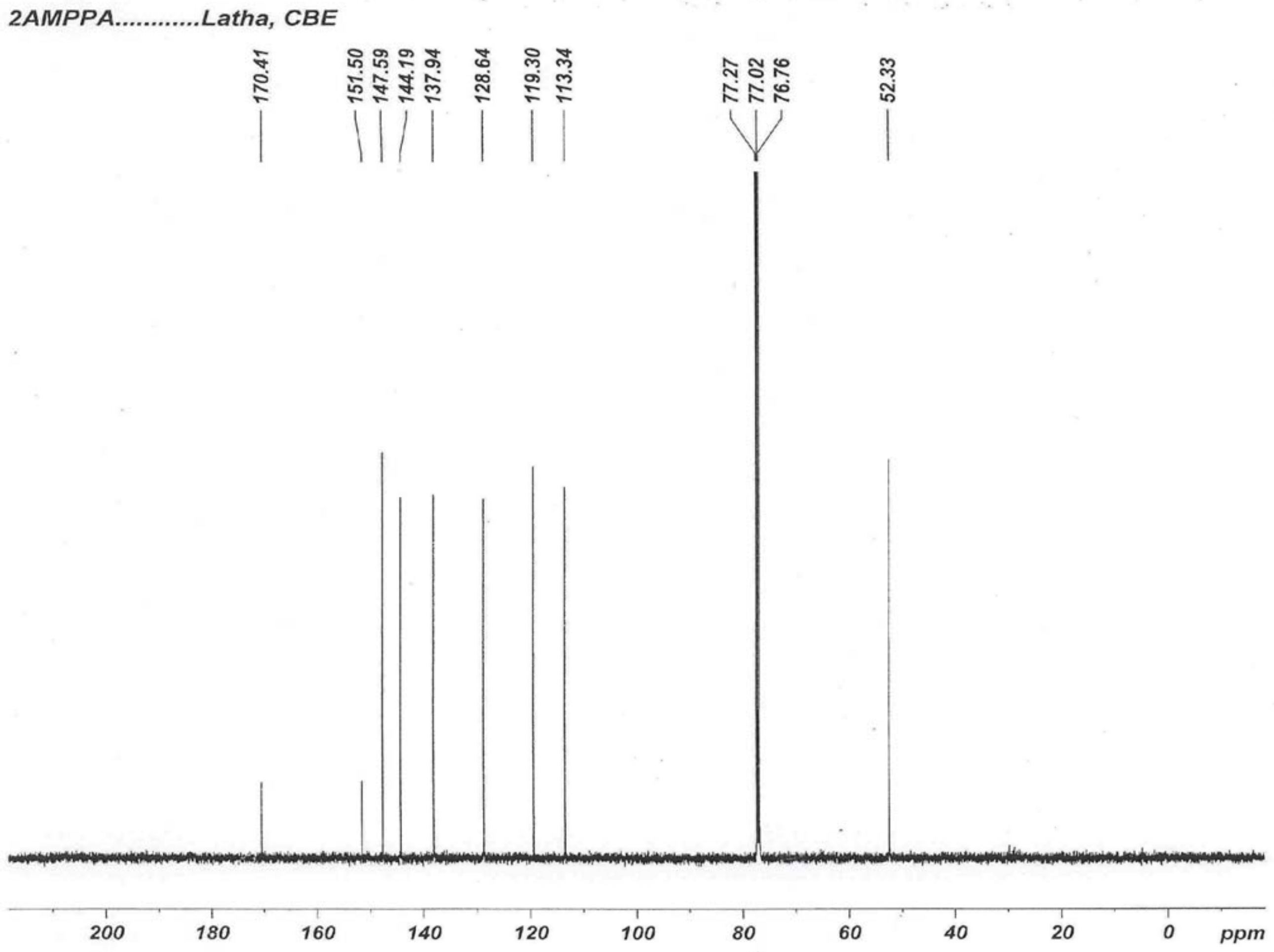


FIGURE - 20

^{13}CNMR SPECTRUM OFPYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



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PROCNO                     1

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PULPROG              zgpg30
TD                     32768
SOLVENT                CDCl3
NS                      1024
DS                         4
SWH                29761.904 Hz
FIDRES              0.908261 Hz
AQ                 0.5505524 sec
RG                       203
DW                    16.800 usec
DE                      6.00 usec
TE                     297.3 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                      7.80 usec
PL1                     0.00 dB
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL12                   17.50 dB
PL13                   17.50 dB
PL2                     0.00 dB
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                     32768
SF               125.7577890 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```
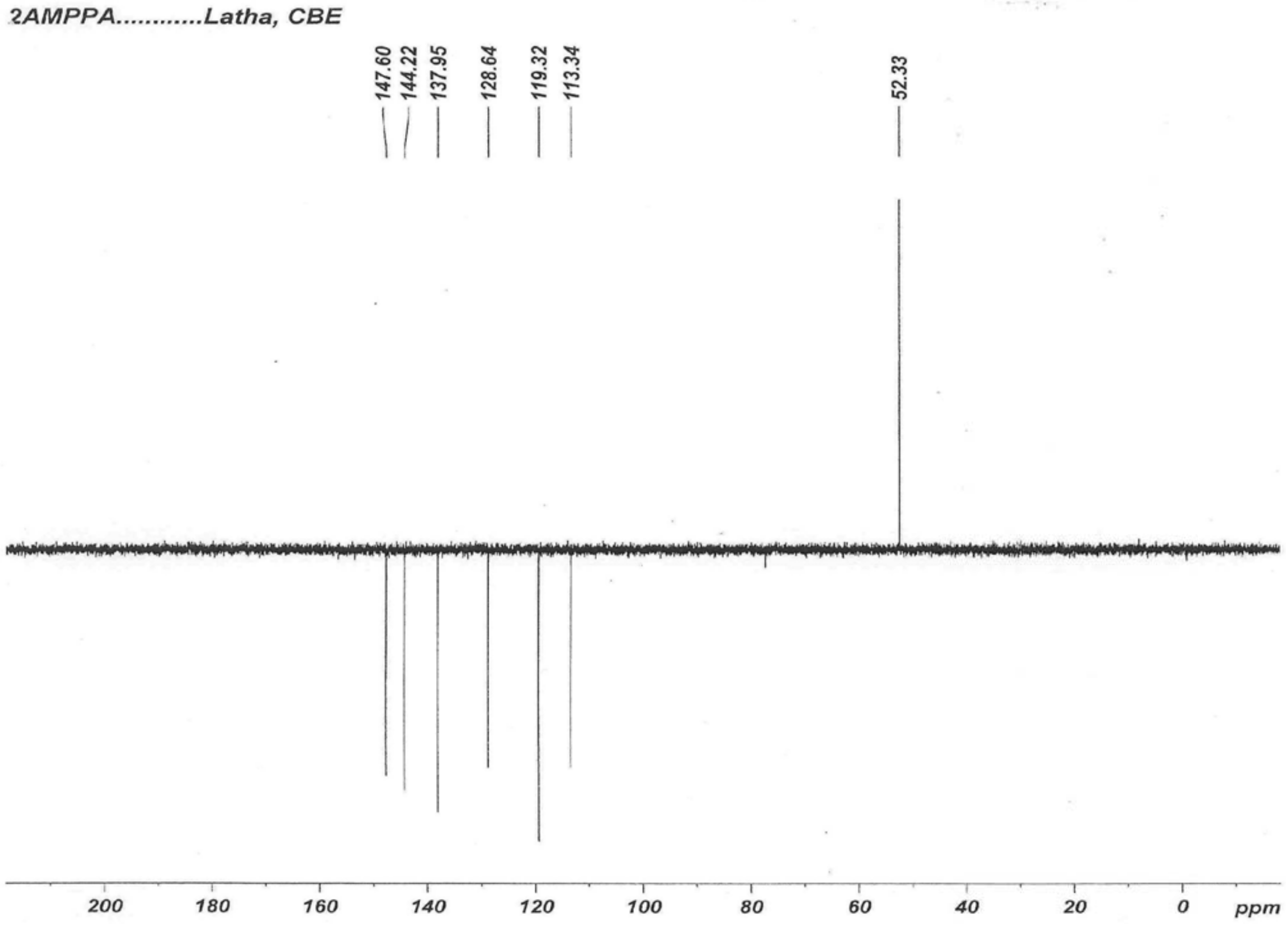

FIGURE - 21

DEPT SPECTRUM OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



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PROCNO                 1

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PULPROG          dept135
TD                 32768
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.00 usec
TE                 295.8 K
CNST2        145.0000000
D1            2.00000000 sec
d12           0.00002000 sec
d2            0.00344828 sec
DELTA         0.00000993 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
p2                 15.60 usec
PL1                 0.00 dB
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
P3                 10.65 usec
p4                 21.30 usec
PCPD2              80.00 usec
PL12               17.50 dB
PL2                 0.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

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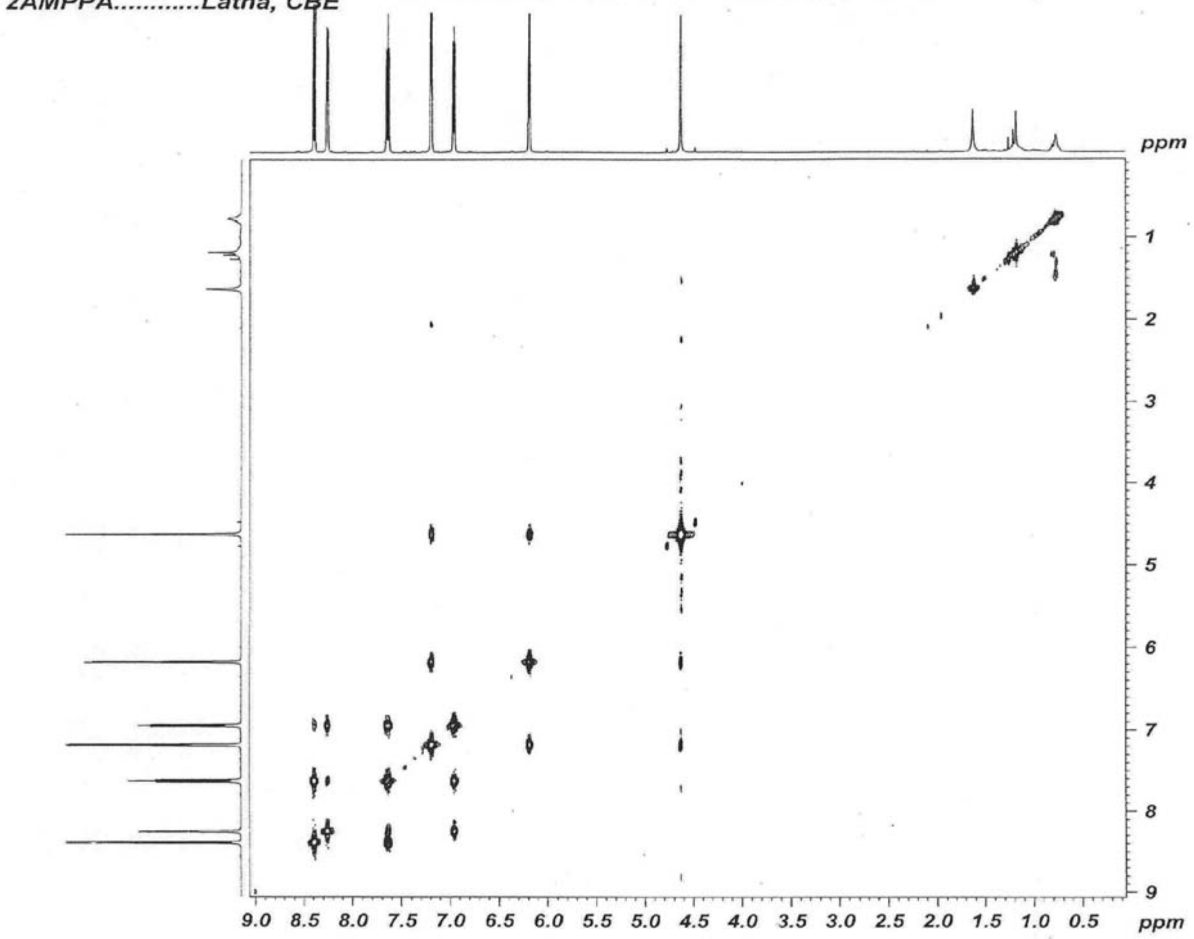
FIGURE -22

COSY SPECTRUM OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



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PROCNO                 1

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PULPROG         cosygpqf
TD                  2048
SOLVENT            CDCl3
NS                     1
DS                     8
SWH             4504.504 Hz
FIDRES          2.199465 Hz
AQ             0.2273780 sec
RG                   203
DW               111.000 usec
DE                  6.00 usec
TE                 296.7 K
d0            0.00000300 sec
D1            1.41275406 sec
d13           0.00000400 sec
D16           0.00020000 sec
INC           0.00022200 sec

======== CHANNEL f1 ========
NUC1                  1H
P0                 10.65 usec
P1                 10.65 usec
PL1                 0.00 dB
SFO1         500.1323186 MHz

====== GRADIENT CHANNEL =====
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1               10.00 %
GPZ2               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
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TD                   128
SFO1            500.1323 MHz
FIDRES         35.191441 Hz
SW                 9.007 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300390 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300390 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
```
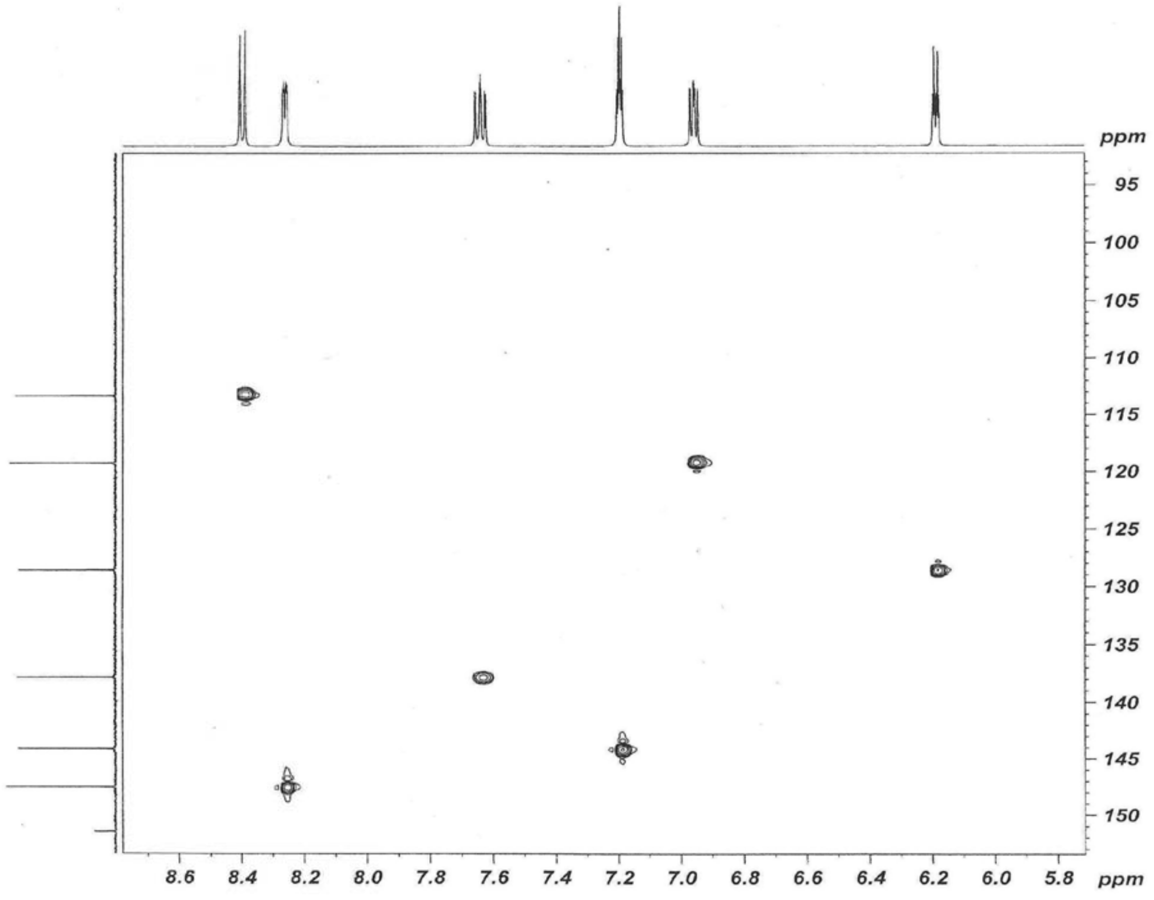

FIGURE - 23

2AMPPA............Latha, CBE

HETCOR SPECTRUM OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



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PROCNO                 1

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PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     2
DS                    16
SWH             4504.504 Hz
FIDRES          4.398930 Hz
AQ             0.1137140 sec
RG                   203
DW               111.000 usec
DE                  6.00 usec
TE                 295.9 K
CNST2        145.0000000
d0            0.00000300 sec
D1            1.46293104 sec
d11           0.03000000 sec
d13           0.00000400 sec
D16           0.00020000 sec
d4            0.00172414 sec
DELTA         0.00122730 sec
DELTA1        0.00071614 sec
INC           0.00002400 sec
ST1CNT               128
ZGOPTNS

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
p2                 21.30 usec
P28                 0.00 usec
PL1                 0.00 dB
SFO1         500.1323186 MHz

======== CHANNEL f2 ========
CPDPRG2             garp
NUC2                 13C
P3                  7.80 usec
p4                 15.50 usec
PCPD2              65.00 usec
PL12               18.00 dB
PL2                 0.00 dB
SFO2         125.7671682 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
ND0                    2
TD                   256
SFO1            125.7672 MHz
FIDRES         81.380211 Hz
SW               165.650 ppm
FnMODE      Echo-Antiecho

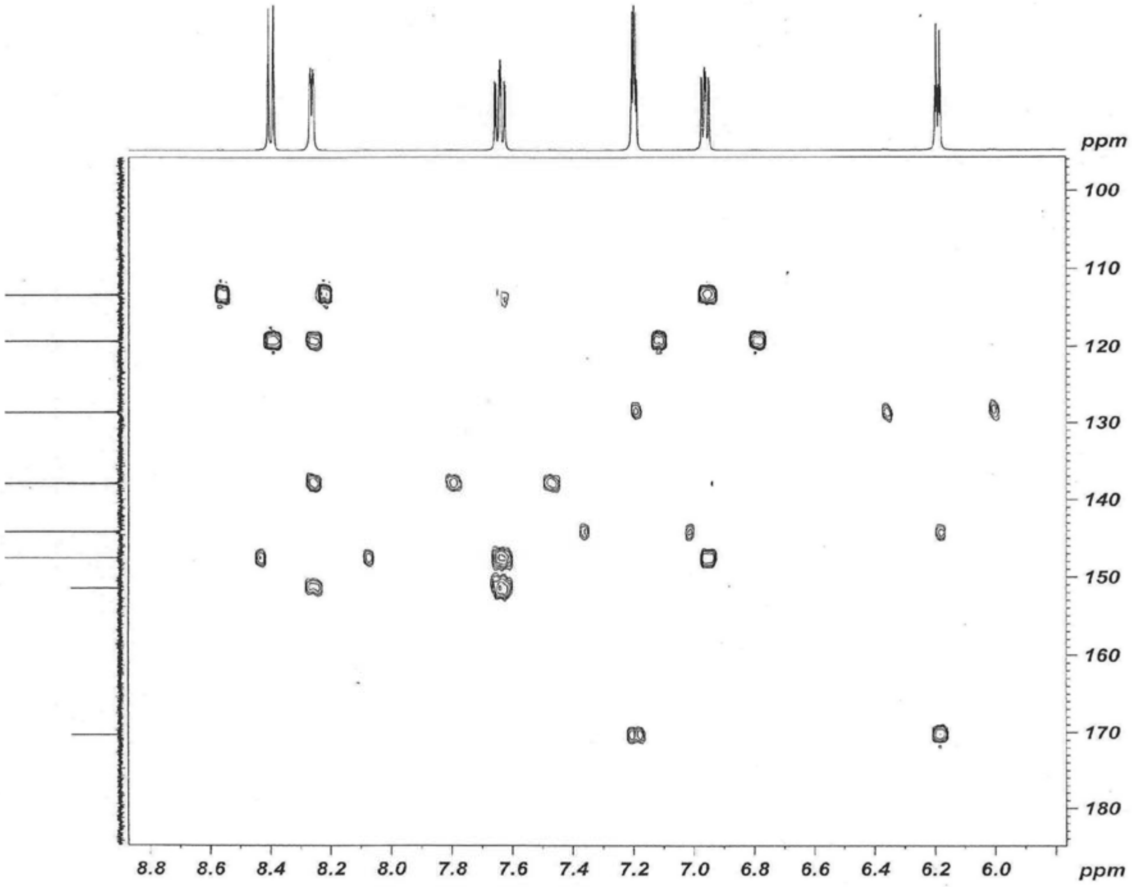
F2 - Processing parameters
SI                  1024
SF           500.1300390 MHz
WDW                QSINE
SSB                    2
LB                  0.00 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577890 MHz
WDW                QSINE
SSB                    2
LB                  0.00 Hz
GB                     0
```

116

FIGURE - 24

2AMPPA............Latha, CBE **HMBC SPECTRUM OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE**



```
Current Data Parameters
NAME              Jul21-2009
EXPNO                     13
PROCNO                     1

F2 - Acquisition Parameters
Date_               20090721
Time                   14.40
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG          hmbcgpndqf
TD                      4096
SOLVENT                CDCl3
NS                         8
DS                        16
SWH                 4504.504 Hz
FIDRES              1.099733 Hz
AQ                 0.4547060 sec
RG                       203
DW                   111.000 usec
DE                      6.00 usec
TE                     296.0 K
CNST13             8.0000000
d0                0.00000300 sec
D1                1.35254395 sec
D16               0.00020000 sec
d6                0.06250000 sec
IN0               0.00001790 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     10.65 usec
p2                     21.30 usec
PL1                     0.00 dB
SFO1             500.1323186 MHz

======== CHANNEL f2 ========
NUC2                     13C
P3                      7.80 usec
PL2                     0.00 dB
SFO2             125.7703443 MHz

====== GRADIENT CHANNEL =====
GPNAM1              SINE.100
GPNAM2              SINE.100
GPNAM3              SINE.100
GPZ1                   50.00 %
GPZ2                   30.00 %
GPZ3                   40.10 %
P16                  1000.00 usec

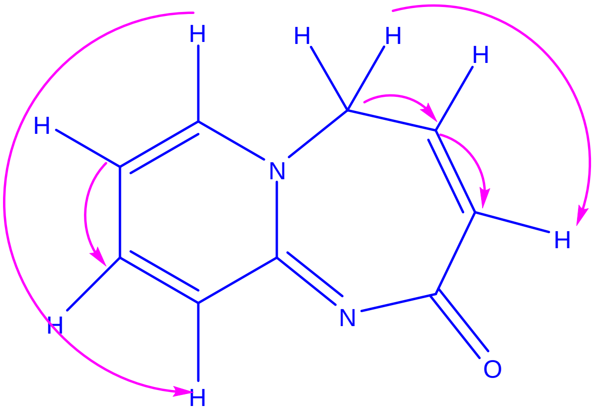
F1 - Acquisition parameters
NDO                        2
TD                       128
SFO1                125.7703 MHz
FIDRES            218.226257 Hz
SW                   222.095 ppm
FnMODE                    QF

F2 - Processing parameters
SI                      1024
SF               500.1300390 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2                       QF
SF               125.7577890 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
```

FIGURE–25

COSY CORRELATIONS OBSERVED IN PYRIDO[1,2-a][1,3] DIAZEPIN-2(5H)-ONE



FIGURE– 26

HMBC CORRELATIONS OBSERVED IN PYRIDO[1,2-a][1,3] DIAZEPIN-2(5H)-ONE

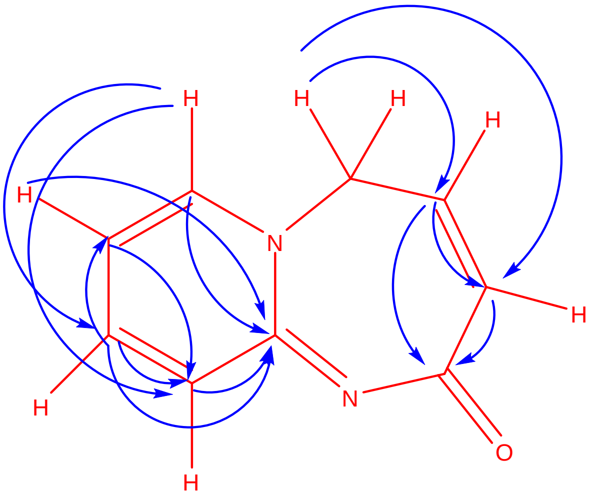


FIGURE -27

MASS SPECTRUM OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE

Sample ID: 2 AMPY / MeOH **Acquired at 14-Jan-200910:23:52**

Hit	Compound Name	Formula	M.W.
1	PTERIDINE, 6,7-DIMETHYL-	C8H8N4	160
2	2,3-DIMETHYL-1-INDOLIZINYL ACETATE $$ 1-INDOLIZINOL,	C12H13O2N	203
3	PENTACYCLO[5.3.0.0(2,6).0(4,10).0(5,8)]DECAN-3,9-DIONE	C10H8O2	160
4	S-TRIAZOLO[4,3-A]PYRIDINE, 3,5,7-TRIMETHYL- (CAS) $$ 3,5	C9H11N3	161
5	S-TRIAZOLO 4,3-A PYRIDINE, 3,5,7-TRIMETHYL-	C9H11N3	161
6	7-METHYL-1,2-DIHYDROQUINOXALIN-2-ONE	C9H8ON2	160
7	TRICYCLO 4.2.2.02,5 DEC-9-ENE-3,7-DICARBONITRILE	C12H12N2	184
8	PYRIDO 2,3-B PYRAZINE	C7H5N3	131
9	ANTI-TRICYCLO[5.2.1.0(2,5)]DECA-3,7-DIEN-9,10-DIONE	C10H8O2	160
10	2-PYRIDINECARBONITRILE	C6H4N2	104
11	1H-INDOLE-2,3-DIONE, 5-METHYL-	C9H7O2N	161
12	TRICYCLO 3.3.1.02,8 NONA-3,6-DIEN-9-ONE	C9H8O	132
13	4(1H)-QUINAZOLINONE, 1-METHYL-	C9H8ON2	160
14	BICYCLO[4.2.0]OCTA-2,4-DIENE-7-CARBONITRILE (CAS)	C9H9N	131
15	BENZENE, (2-PROPYNYLOXY)-	C9H8O	132
16	TRICYCLO 4.2.2.02,5 DEC-9-ENE-7,8-DICARBOXYLIC ANHYD	C13H11O3N	229
17	6 METHYL COUMARIN	C10H8O2	160
18	3-METHYL-2H-CYCLOHEPTA[B]FURAN-2-ONE $$ 2H-CYCLOH	C10H8O2	160
19	8-METHYLCOUMARIN $$ 2H-1-BENZOPYRAN-2-ONE, 8-METH	C10H8O2	160
20	4H-PYRIDO[1,2-A]PYRIMIDIN-4-ONE, 2-METHYL- (CAS) $$ 2-M	C9H8ON2	160

Sample ID: 2 AMPY / MeOH **Acquired on 14-Jan-2009 at 10:23:52**
Reverse fit factor [REV]: 589

EM-282 1318 (15.189) Rf (3,6.000)

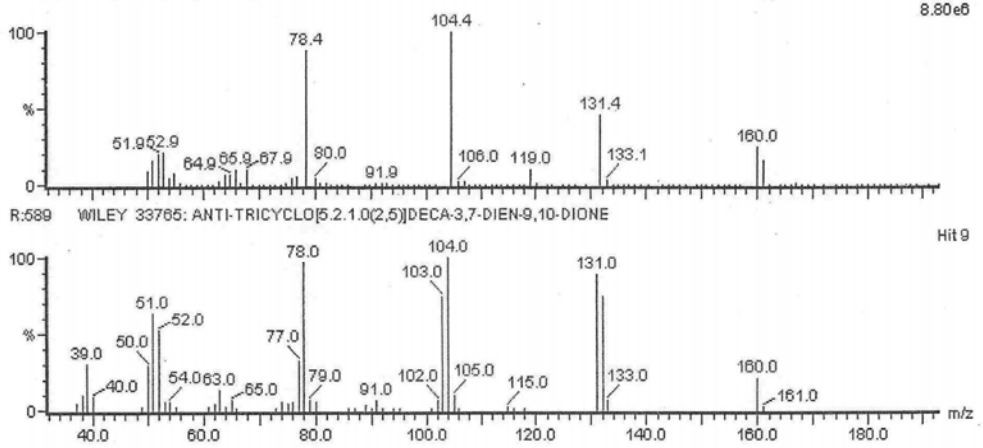
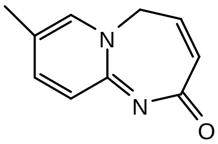
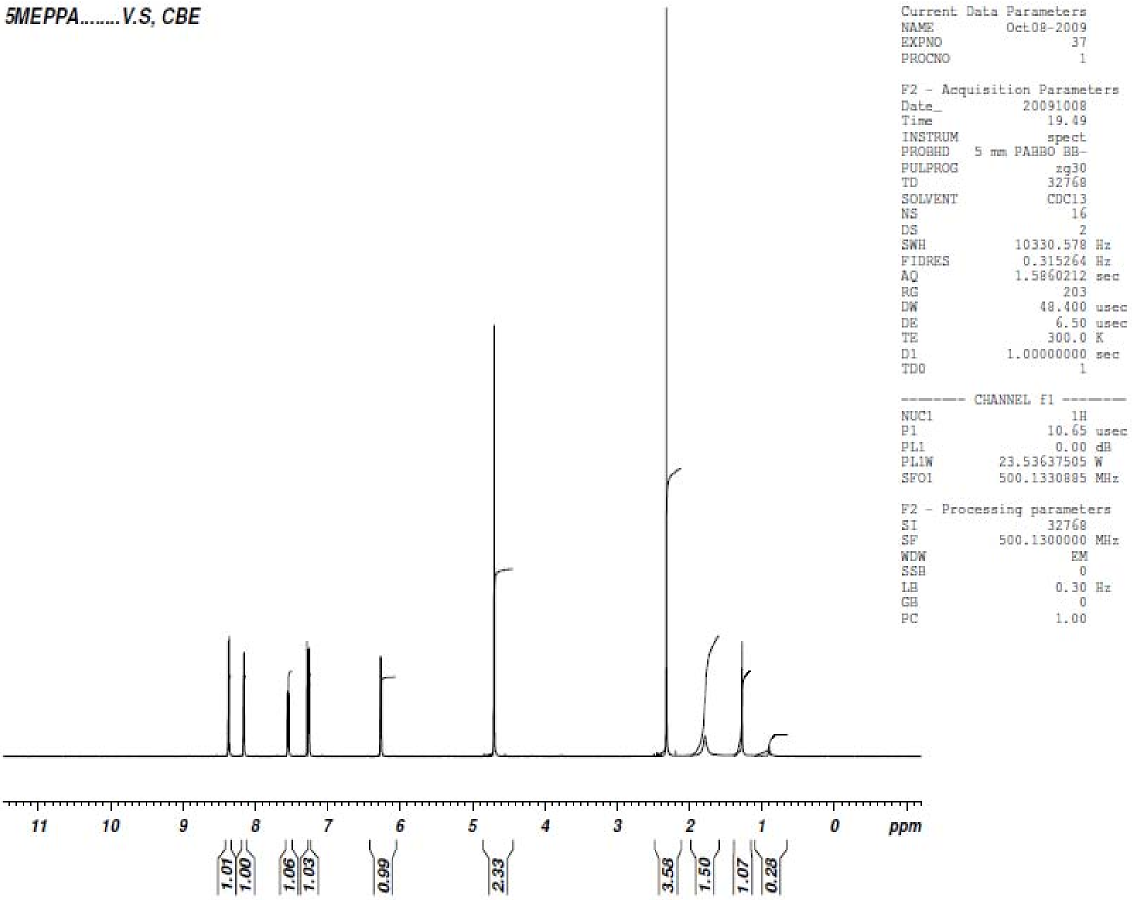


FIGURE -28

^{1}HNMR SPECTRUM OF 7-METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE





```
Current Data Parameters
NAME          Oct08-2009
EXPNO                 37
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091008
Time               19.49
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10330.578 Hz
FIDRES          0.315264 Hz
AQ             1.5860212 sec
RG                   203
DW                48.400 usec
DE                  6.50 usec
TE                 300.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
PL1                 0.00 dB
PL1W         23.53637505 W
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

FIGURE -28a

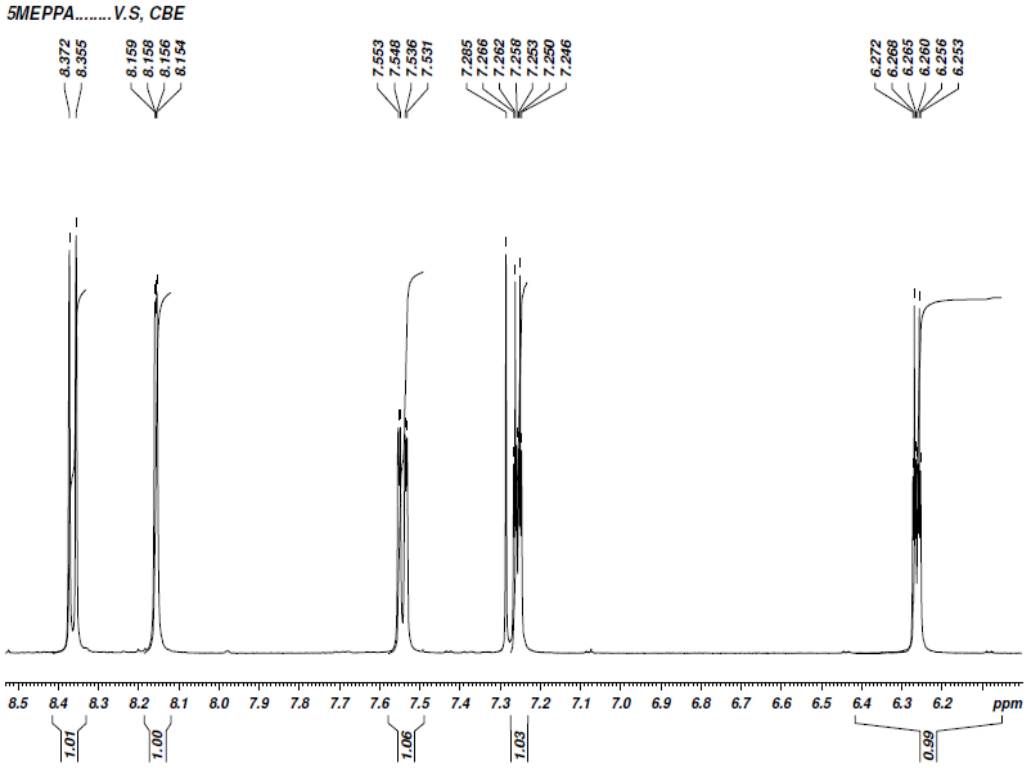
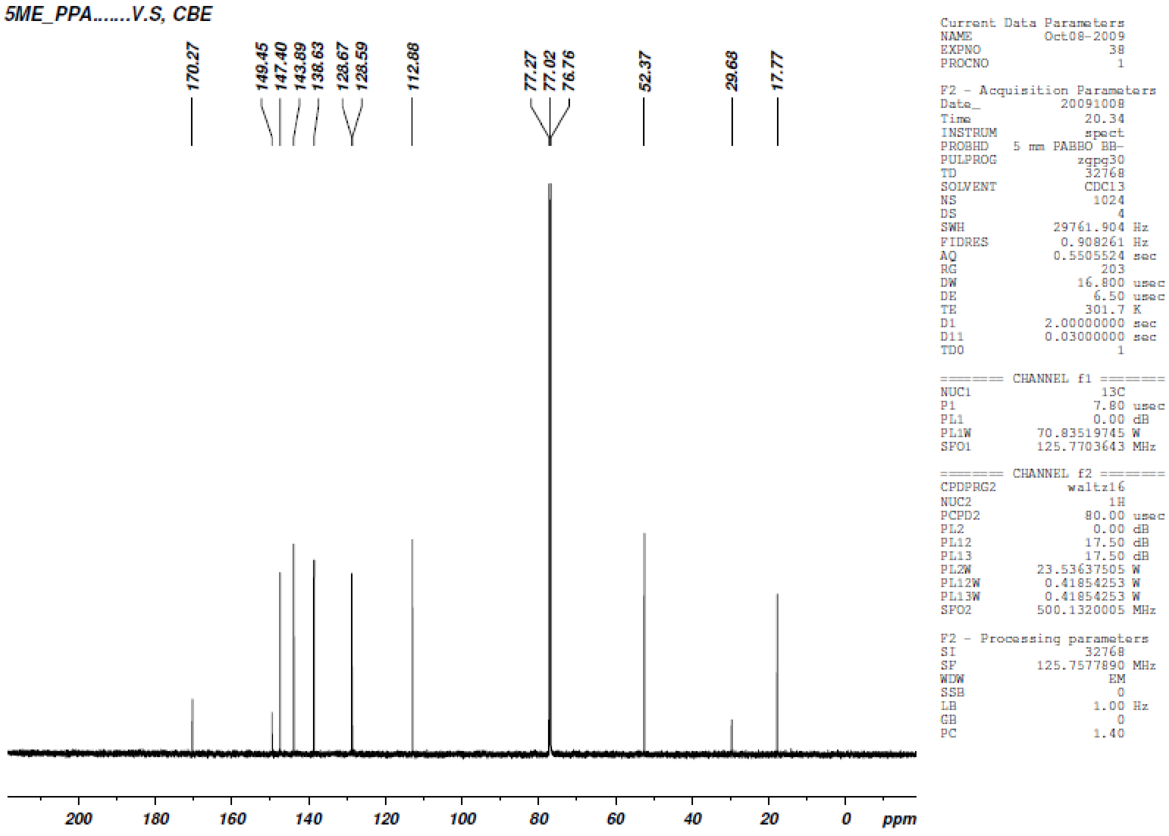

5MEPPA.......V.S, CBE
8.372
8.355
8.159
8.158
8.156
8.154
7.553
7.548
7.536
7.531
7.285
7.266
7.262
7.258
7.253
7.250
7.246
6.272
6.268
6.265
6.260
6.256
6.253
8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 ppm
1.01
1.00
1.06
1.03
0.99

FIGURE -29

^{13}CNMR SPECTRUM OF 7-METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



```
Current Data Parameters
NAME            Oct08-2009
EXPNO                   38
PROCNO                   1

F2 - Acquisition Parameters
Date_             20091008
Time                 20.34
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   32768
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH              29761.904 Hz
FIDRES            0.908261 Hz
AQ               0.5505524 sec
RG                     203
DW                  16.800 usec
DE                    6.50 usec
TE                   301.7 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

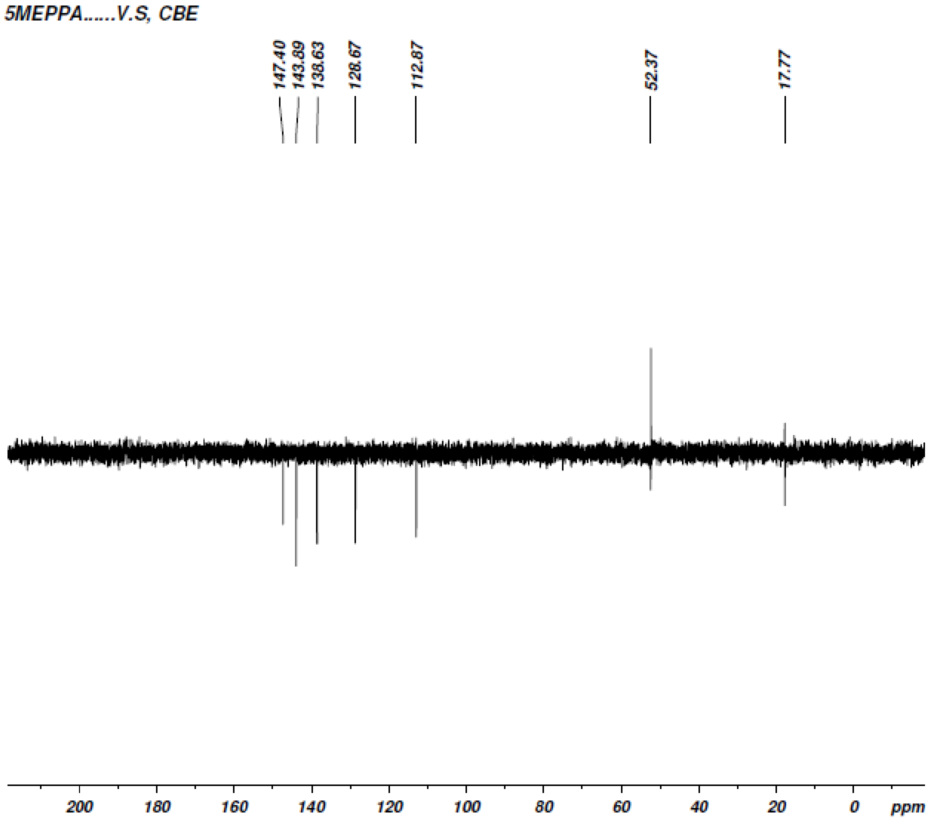
======== CHANNEL f1 ========
NUC1                   13C
P1                    7.80 usec
PL1                   0.00 dB
PL1W           70.83519745 W
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 17.50 dB
PL13                 17.50 dB
PL2W           23.53637505 W
PL12W           0.41854253 W
PL13W           0.41854253 W
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                   32768
SF             125.7577890 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

FIGURE -30

DEPT SPECTRUM OF 7-METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



```
Current Data Parameters
NAME          Oct09-2009
EXPNO                 28
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091009
Time               17.50
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG         dept135
TD                32768
SOLVENT            CDCl3
NS                   512
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.50 usec
TE                 301.3 K
CNST2        145.0000000
D1            2.00000000 sec
D2            0.00344828 sec
D12           0.00002000 sec
TD0                    1

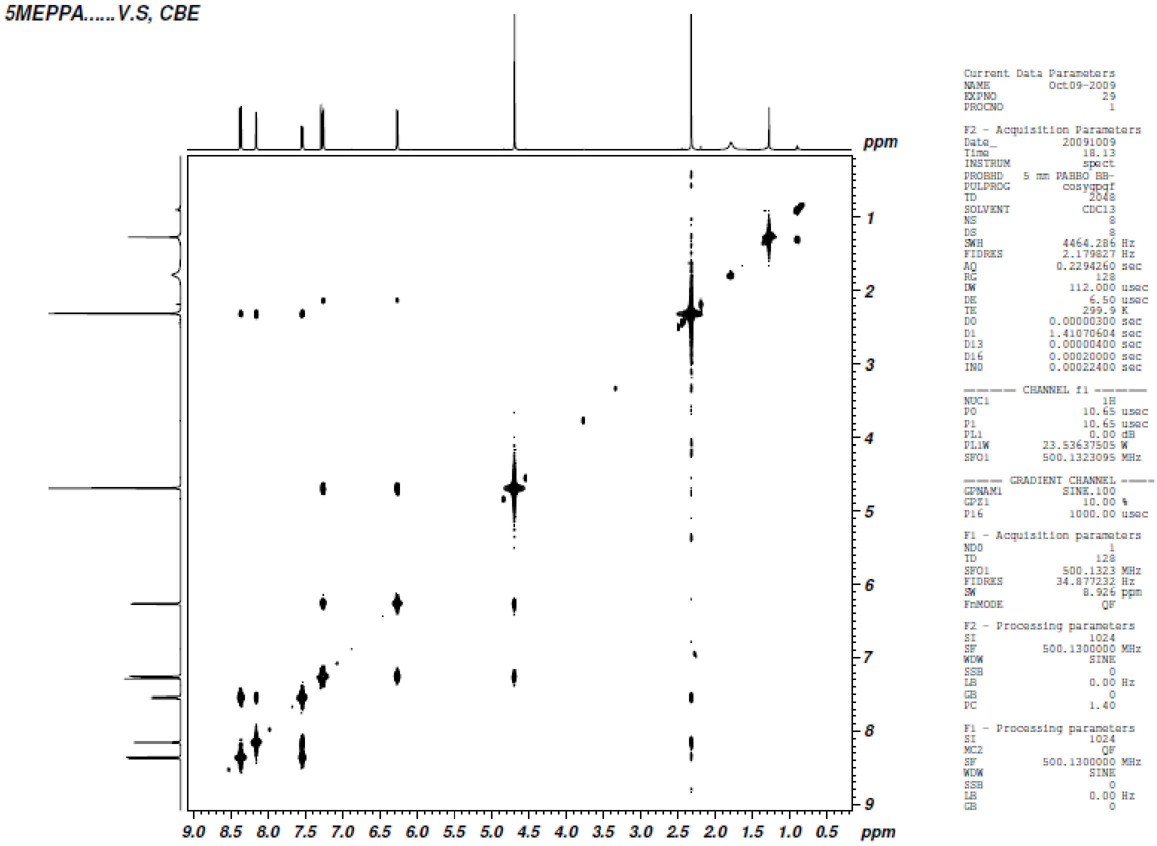
======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
P2                 15.60 usec
PL1                 0.00 dB
PL1W         70.83519745 W
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
P3                 10.65 usec
P4                 21.30 usec
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               17.50 dB
PL2W         23.53637505 W
PL12W         0.41854253 W
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

FIGURE -31

COSY SPECTRUM OF 7-METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



```
Current Data Parameters
NAME          Oct09-2009
EXPNO                 29
PROCNO                 1

F2 - Acquisition Parameters
Date_           20091009
Time               18.13
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG         cosygpqf
TD                  2048
SOLVENT            CDCl3
NS                     8
DS                     8
SWH             4464.286 Hz
FIDRES          2.179827 Hz
AQ             0.2294260 sec
RG                   128
DW               112.000 usec
DE                  6.50 usec
TE                 299.9 K
D0            0.00000300 sec
D1            1.41070604 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00022400 sec

======== CHANNEL f1 ========
NUC1                  1H
P0                 10.65 usec
P1                 10.65 usec
PL1                 0.00 dB
PL1W         23.53637505 W
SFO1        500.1323095 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPZ1               10.00 %
P16              1000.00 usec

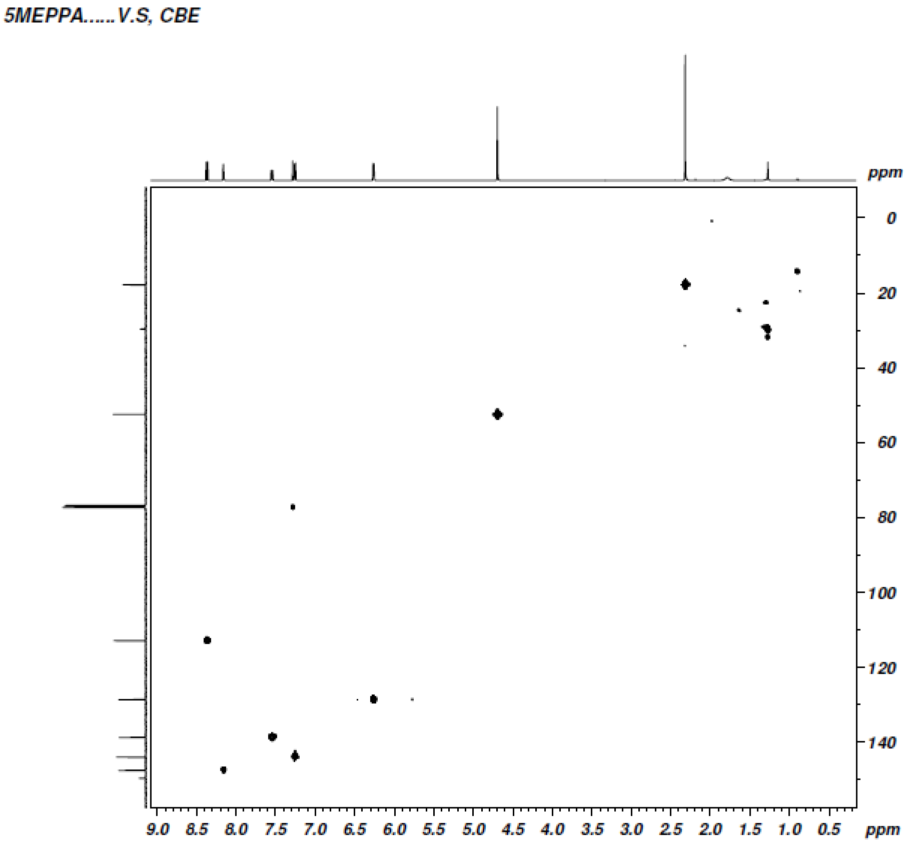
F1 - Acquisition parameters
ND0                    1
TD                   128
SFO1            500.1323 MHz
FIDRES         34.877232 Hz
SW                 8.926 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300000 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300000 MHz
WDW                 SINE
SSB                    0
LB                  0.00 Hz
GB                     0
```

FIGURE -32

HETCOR SPECTRUM OF 7-METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



```
Current Data Parameters
NAME       Oct09-2009
EXPNO            30
PROCNO            1

F2 - Acquisition Parameters
Date_        20091009
Time           18.43
INSTRUM         spect
PROBHD   5 mm PABBO BB-
PULPROG       hsqcetgp
TD             1024
SOLVENT        CDCl3
NS                8
DS               16
SWH         4464.286 Hz
FIDRES      4.359654 Hz
AQ        0.1147380 sec
RG              203
DW          112.000 usec
DE             6.50 usec
TE            299.6 K
CNST2     145.0000000
D0       0.00000300 sec
D1       1.46190703 sec
D4       0.00172414 sec
D11      0.03000000 sec
D13      0.00000400 sec
D16      0.00020000 sec
IN0      0.00002400 sec
ZGOPTNS

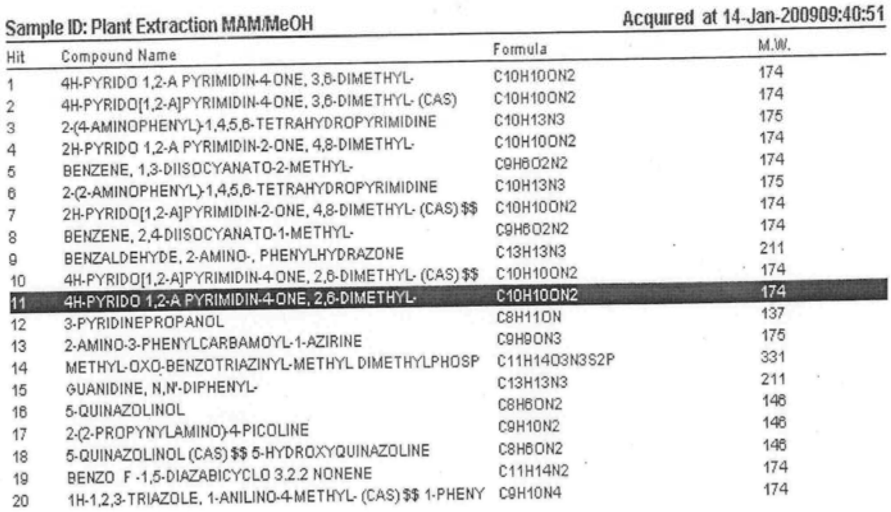
======== CHANNEL f1 ========
NUC1             1H
P1          10.65 usec
P2          21.30 usec
P28          0.00 usec
PL1          0.00 dB
PL1W    23.53637505 W
SFO1    500.1323095 MHz

======== CHANNEL f2 ========
CPDPRG2          garp
NUC2             13C
P3           7.80 usec
P4          15.60 usec
PCPD2        65.00 usec
PL2          0.00 dB
PL12        18.00 dB
PL2W    70.83519745 W
PL12W    1.12266219 W
SFO2    125.7671682 MHz

====== GRADIENT CHANNEL =====
GPNAM1        SINE.100
GPNAM2        SINE.100
GPZ1          80.00 %
```

FIGURE-33

MASS SPECTRUM OF 7-METHYL PYRIDO[1,2-2][1,3]DIAZEPIN-2(5H)-ONE



Sample ID: Plant Extraction MAM/MeOH **Acquired at 14-Jan-200909:40:51**

Hit	Compound Name	Formula	M.W.
1	4H-PYRIDO 1,2-A PYRIMIDIN-4-ONE, 3,6-DIMETHYL-	C10H10ON2	174
2	4H-PYRIDO[1,2-A]PYRIMIDIN-4-ONE, 3,6-DIMETHYL- (CAS)	C10H10ON2	174
3	2-(4-AMINOPHENYL)-1,4,5,6-TETRAHYDROPYRIMIDINE	C10H13N3	175
4	2H-PYRIDO 1,2-A PYRIMIDIN-2-ONE, 4,8-DIMETHYL-	C10H10ON2	174
5	BENZENE, 1,3-DIISOCYANATO-2-METHYL-	C9H6O2N2	174
6	2-(2-AMINOPHENYL)-1,4,5,6-TETRAHYDROPYRIMIDINE	C10H13N3	175
7	2H-PYRIDO[1,2-A]PYRIMIDIN-2-ONE, 4,8-DIMETHYL- (CAS) $$	C10H10ON2	174
8	BENZENE, 2,4-DIISOCYANATO-1-METHYL-	C9H6O2N2	174
9	BENZALDEHYDE, 2-AMINO-, PHENYLHYDRAZONE	C13H13N3	211
10	4H-PYRIDO[1,2-A]PYRIMIDIN-4-ONE, 2,6-DIMETHYL- (CAS) $$	C10H10ON2	174
11	4H-PYRIDO 1,2-A PYRIMIDIN-4-ONE, 2,6-DIMETHYL-	C10H10ON2	174
12	3-PYRIDINEPROPANOL	C8H11ON	137
13	2-AMINO-3-PHENYLCARBAMOYL-1-AZIRINE	C9H9ON3	175
14	METHYL-OXO-BENZOTRIAZINYL-METHYL DIMETHYLPHOSP	C11H14O3N3S2P	331
15	GUANIDINE, N,N'-DIPHENYL-	C13H13N3	211
16	5-QUINAZOLINOL	C8H6ON2	146
17	2-(2-PROPYNYLAMINO)-4-PICOLINE	C9H10N2	146
18	5-QUINAZOLINOL (CAS) $$ 5-HYDROXYQUINAZOLINE	C8H6ON2	146
19	BENZO F -1,5-DIAZABICYCLO 3.2.2 NONENE	C11H14N2	174
20	1H-1,2,3-TRIAZOLE, 1-ANILINO-4-METHYL- (CAS) $$ 1-PHENY	C9H10N4	174

Sample ID: Plant Extraction MAM/MeOH

Acquired on 14-Jan-2009 at 09:40:
Reverse fit factor [REV]: 6

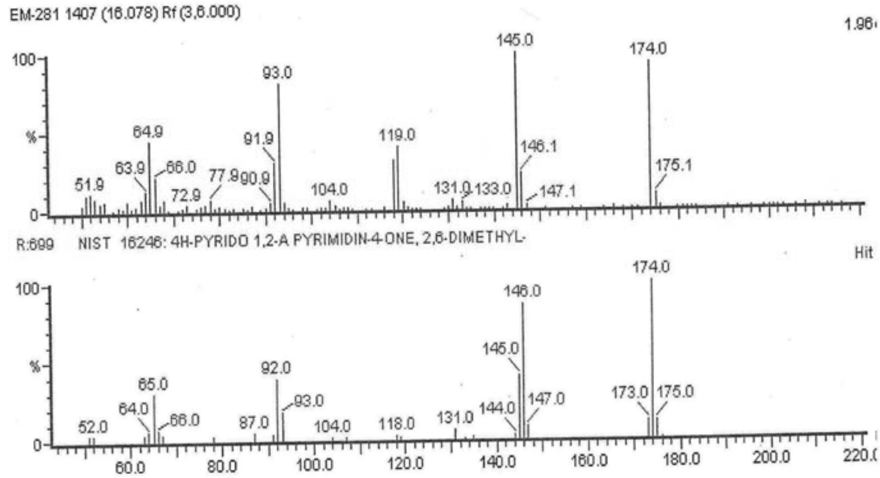
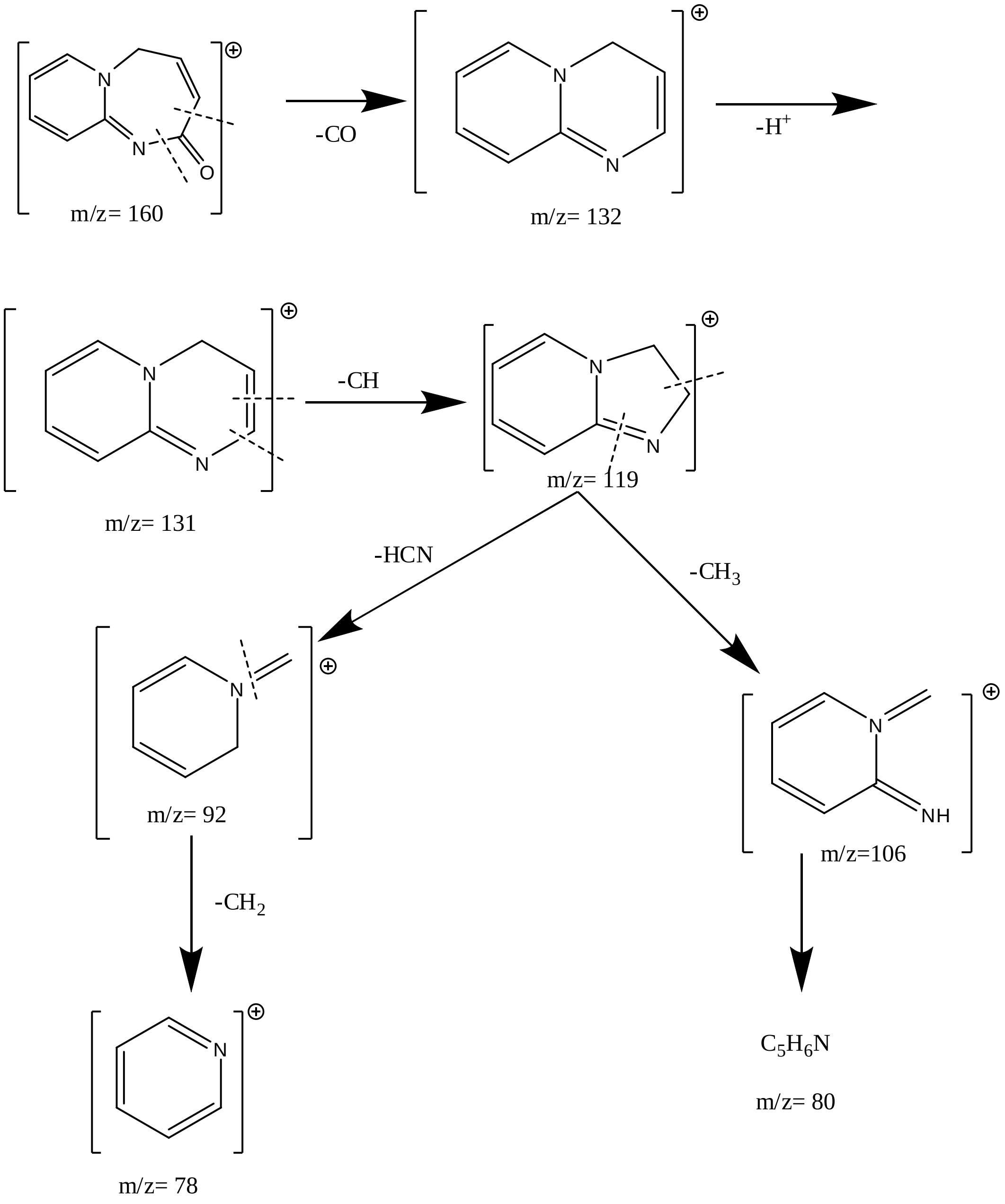


CHART- 2

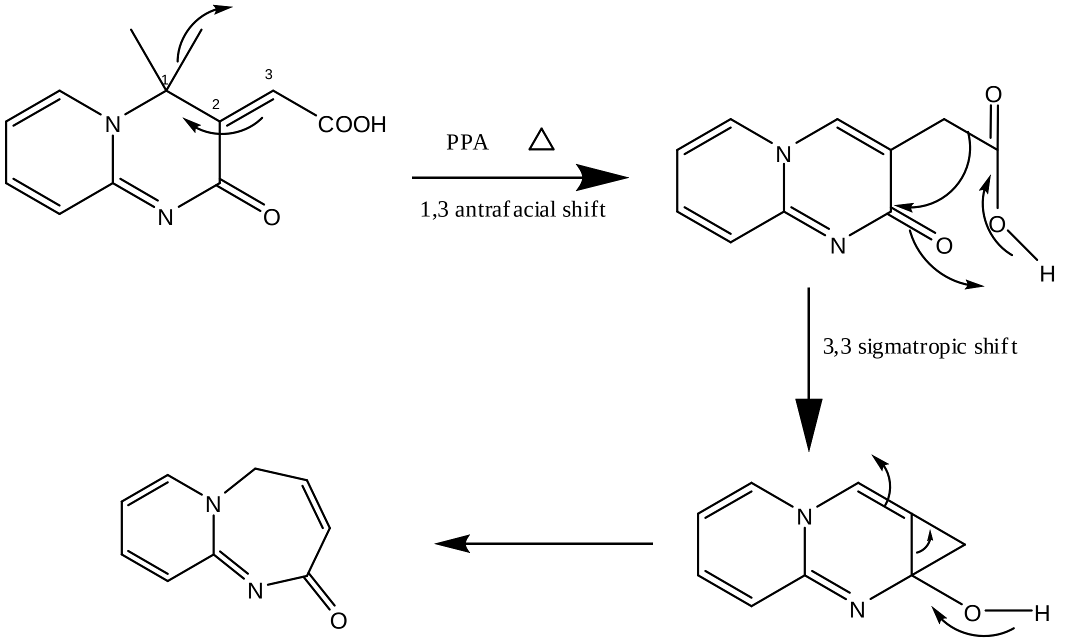
MASS FRAGMENTATION PATTERN OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



Possible mechanism for the formation of pyrido[1,2-a][1,3]diazepin-2(5H)-one is given in scheme – 6.

SCHEME – 6

MECHANISM FOR THE FORMATION OF PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE



The compound probably under goes a facile Carroll **(Kirk L. Sorgi et al, 1995)** like rearrangement (S**cheme 6)** involving a 1,3 hydrogen shift in the first step, subsequently followed by a 3,3 sigmatropic shift with decarboxylation to provide pyrido[1,2-a][1,3]diazepin-2(5H)-one.

The NMR data of the compounds 212b and 212c are summarized in the **Tables – 17 and 18.**

TABLE -17

NMR DATA OF -9 METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE-212b

^{1}H Shift in ppm	Multip-licity/no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	Dept 135	C^{13} shift in ppm	Carbon	Dept 135
7.3	d(d)(d)/1	H_3	170	C_2	-C	128.5	C_8	-CH
6.3	d(t)/1	H_4	144	C_3	-CH	113	C_9	-CH
4.7	t/2	H_5	128.6	C_4	-CH	149	C_{10}	-CH
8.2	s/3	H_7	52	C_5	$-CH_2$	149	C_{11}	-C
2.4	d/1	H_8-Me	147	C_6	-CH			
8.4	d(d)/1	H_9	139	C_7	-CH			
7.5	d/1	H_{10}	18	C_7 - Me	$-CH_3$			

TABLE - 18

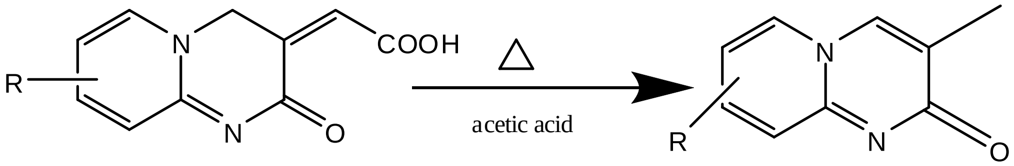
NMR DATA OF 7-METHYL PYRIDO[1,2-a][1,3]DIAZEPIN-2(5H)-ONE

^{1}H Shift in ppm	Multip-licity/no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	Dept 135	C^{13} shift in ppm	Carbon	Dept 135
7.2	d(t)/1	H_3	170	C_2	-C	112	C_9	-CH
6.25	d(t)/1	H_4	144	C_3	-CH	119	C_{10}	-CH
4.7	t/2	H_5	129	C_4	-CH	157	C_{11}	-C
2.5	s/3	H_7 -Me	52	C_5	$-CH_2$			
8.2	d/1	H_8	138	C_7	-C			
7.6	t/1	H_9	24	C_7 -Me	$-CH_3$			
6.8	d/1	H_{10}	110	C_8	-CH			

4.2.2 REACTION WITH GLACIAL ACETIC ACID

The results of the reaction of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene glacial acetic acid with PPA prompted to accomplish similar reaction of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acids with other acids like glacial acetic acid and trifluoro acetic acid.

The reaction of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid with glacial aacetic acid under heat yielded pure white crystals after triturating with pet ether.



209 **213**

Scheme - 7

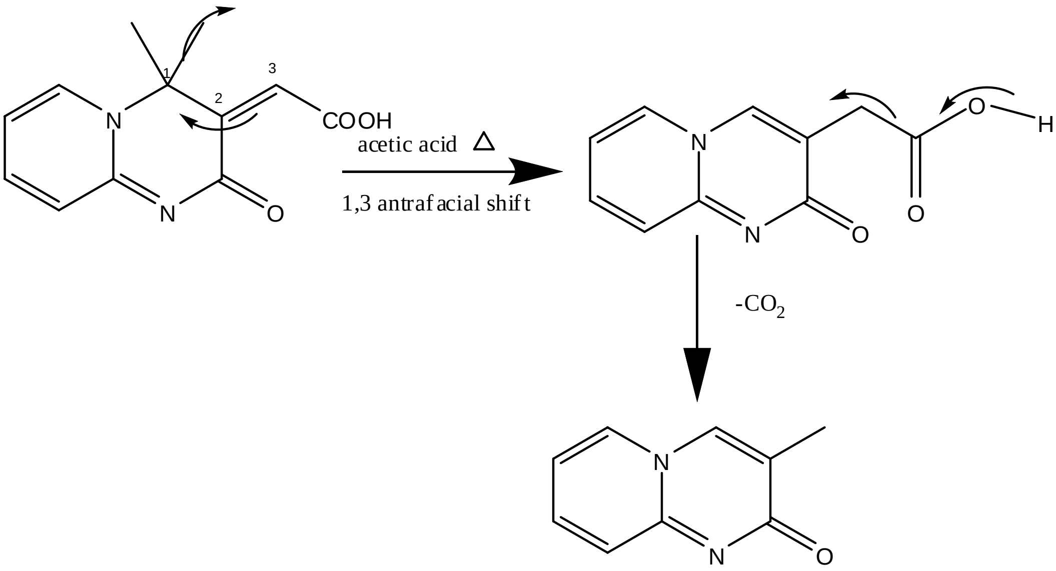
R = H, 3-methyl, 4-methyl, 5-methyl, 6-methyl, 4,6-dimethyl

The structure of the compounds **213a -e** were determined by ^{1}H and ^{13}C NMR analysis. ^{1}HNMR of the product **213a Figure-34** revealed a specific sharp singlet for three protons at δ 2.2ppm. This confirmed the presence of $-CH_3$ moiety in the product. For methyl substituted derivatives an extra methyl signal appeared as a singlet in the range of δ 2 –2.3. The other signals at δ 9.3, 8.2, 7.7, 7.6 were due to protons in the aromatic region of the pyridine nucleus. Further the ^{13}C spectrum **Figure 35** accounted only for nine carbons instead of expected ten carbons indicating the occurrence of decaboxylation. Hence the compound was identified as 3-Me-pyrido-[1,2-a] pyrimidine 2-one.

The reaction can be considered to proceed by 1,3 antrafacial hydrogen shift followed by decarboxylation **Scheme-8** to yield 3-Me-pyrido-[1,2-a] pyrimidin-2-one **213**.

SCHEME -8

MECHANISM FOR THE FORMATION OF 3-ME-PYRIDO-[1,2-a] PYRIMIDIN 2-ONE



The assignment of proton and ^{13}C chemical shifts of the compound 3-Me-pyrido-[1,2-a] pyrimidin 2-ones are presented in the **Tables-19 – 24**

TABLE - 19

NMR DATA OF 3-METHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
2.1	s/3	H_3-Me	169	C_2	151	C_{10}
9.3	s(b)/1	H_4	119	C_3		
8.3	d/1	H_6	24.6	C_3-Me		
7.7	p/1	H_7	147	C_4		
8.2	d/1	H_8	138	C_6 &C_9		
7.1	d(t)d/1	H_9	114	C_7		

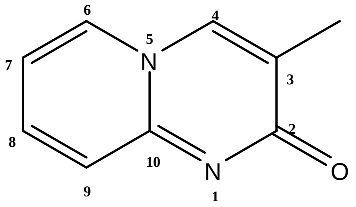


TABLE - 20

NMR DATA OF 3,9-DIMETHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
8.5	s(b)/1	H_4	168	C_2	17	C_9-Me
2.3	s/3	H_3-Me	24	C_3-Me	149	C_{10}
8.2	s/1	H_6	147	C_4		
7.1	q/1	H_7	129	C_6& C_3		
7.5	d/1	H_8	113	C_7		
2.1	s/3	H_9-Me	139	C_8 & C_9		

TABLE - 21

NMR DATA OF 3,8-TRIMETHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity/ no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
2.4	s/1	H_3-Me	169	C_2	111	C_7
8	s(b)/1	H_4	24	C_3-Me	21	C_8-Me
2.3	s/3	H_6-Me	120	C_3 & C_8	156	C_{10}
6.7	s/1	H_7	151	C_4		
2.1	s/3	H_8-Me	123	C_6		
7.8	s/1	H_9	23	C_6-Me		

TABLE -22

NMR DATA OF 3,7-DIMETHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity/ no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
2.3	s/3	H_3-Me	16 8	C_2	18	C_7-Me
8.7	s (b)/1	H_4	114	C_3	149	C_{10}
8.1	s/1	H_6	25	C_3-Me		
2.2	s/3	H_7-Me	147	C_4		
7.5	d(d)/1	H_8	139	C_6& C_8		
8.0	d/1	H_9	129	C_7& C_9		

TABLE - 23

NMR DATA OF 3,6-DIMETHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity/ no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
2.4	s/3	H_3-Me	168	C_2	110	C_7
8.1	s(b)/1	H_4	24	C_3-Me	150	C_{10}
2.1	s/3	H_6-Me	119	C_3 & C_9		
7.6	t/1	H_7	156	C_4		
8.0	d/1	H_8	23	C_6-Me		
6.9	d/1	H_9	138	C_6 & C_8		

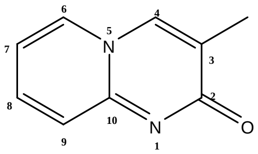
TABLE - 24

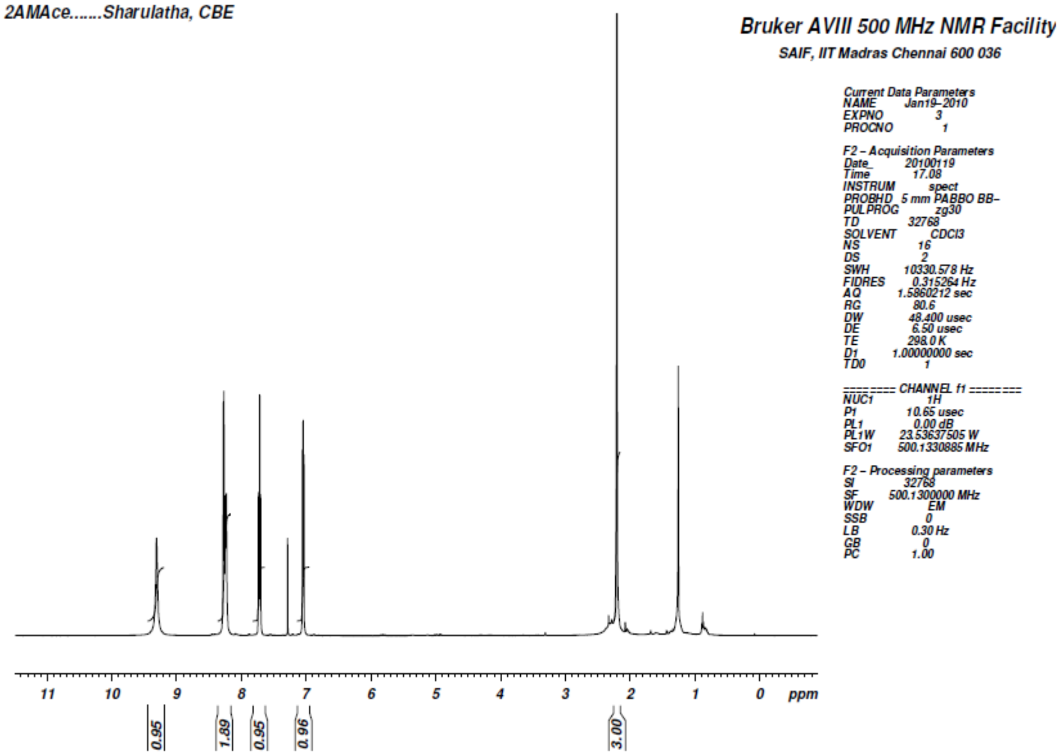
NMR DATA OF 3,6,8-TRIIMETHYL-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity/ no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
2.4	s/1	H_3-Me	169	C_2	111	C_7
8	s(b)/1	H_4	24	C_3-Me	21	C_8-Me
2.3	s/3	H_6-Me	120	C_3 & C_8	156	C_{10}
6.7	s/1	H_7	151	C_4		
2.1	s/3	H_8-Me	123	C_6		
7.8	s/1	H_9	23	C_6-Me		

FIGURE – 34

^{1}H NMR SPECTRUM OF 3-ME-PYRIDO-[1,2-a] PYRIMIDIN-2-ONE





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RG              80.6
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TE             298.0 K
D1       1.00000000 sec
TD0                1

======== CHANNEL f1 ========
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P1             10.65 usec
PL1             0.00 dB
PL1W     23.53637505 W
SFO1     500.1330885 MHz

F2 - Processing parameters
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SF       500.1300000 MHz
WDW               EM
SSB                0
LB              0.30 Hz
GB                 0
PC              1.00
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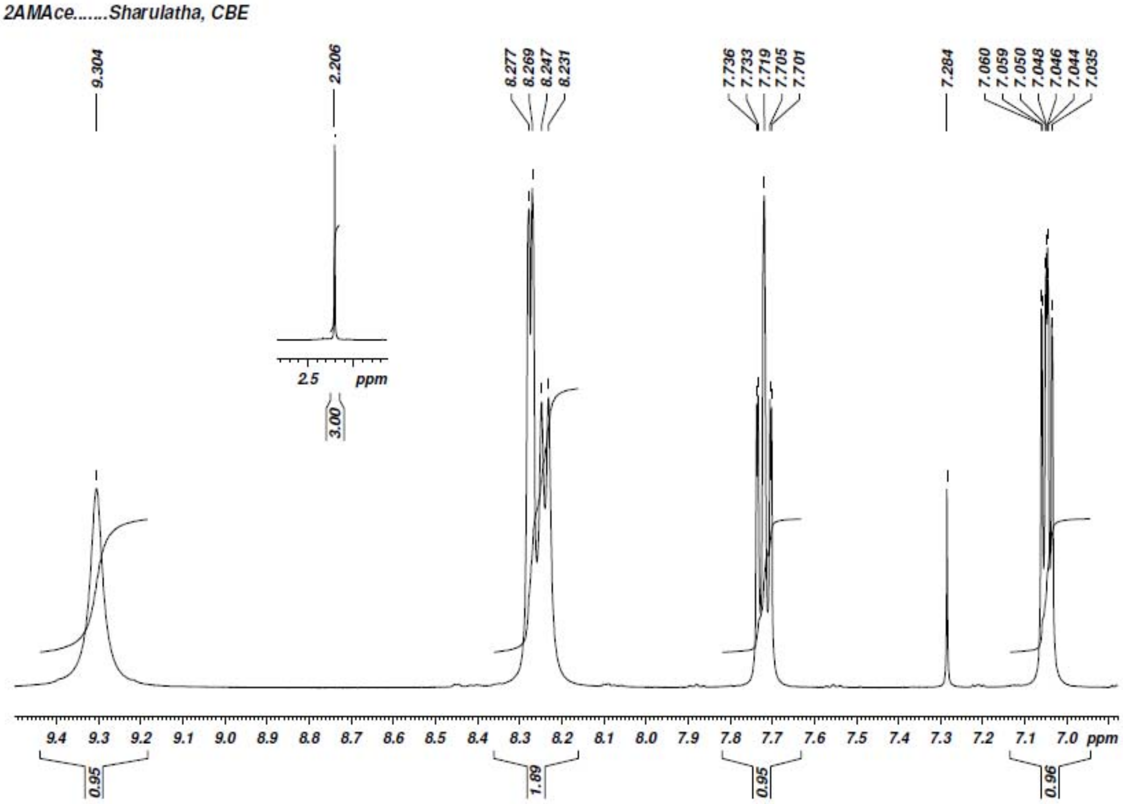
FIGURE – 34a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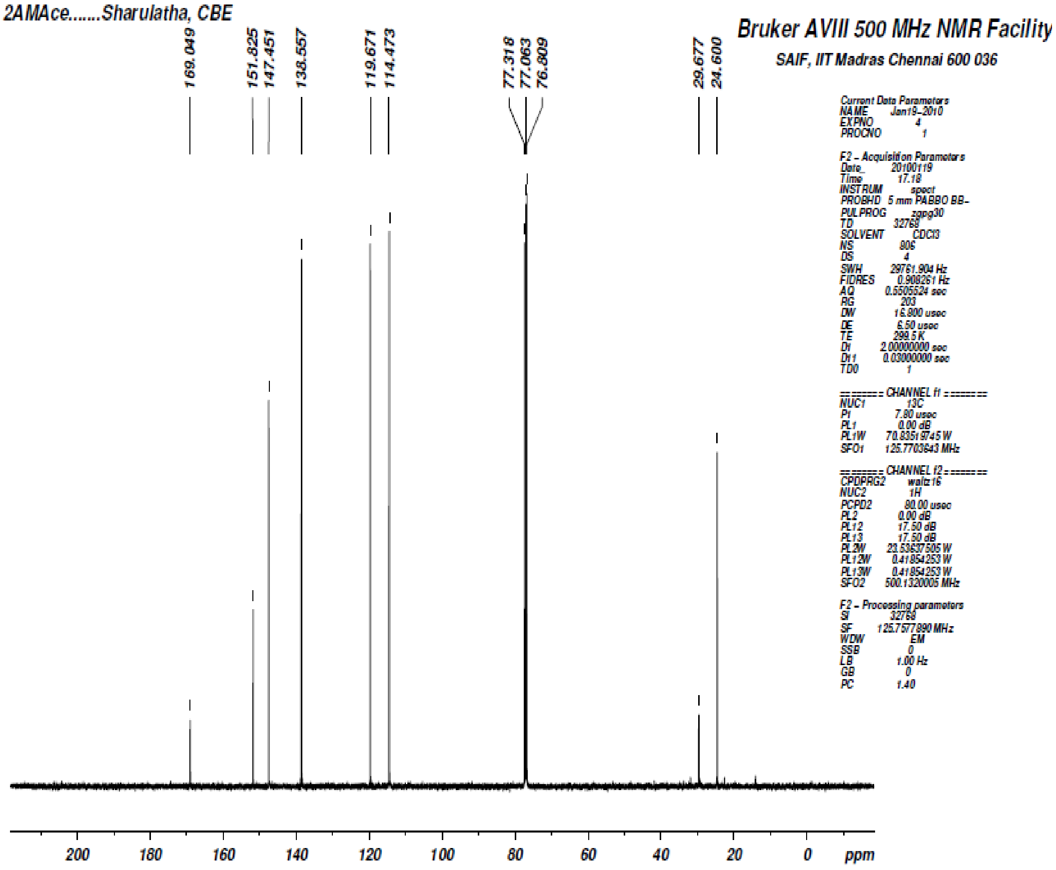
8.277
8.269
8.247
8.231
7.736
7.733
7.719
7.705
7.701
7.284
7.060
7.059
7.050
7.048
7.046
7.044
7.035
2.5
ppm
3.00
9.4
9.3
9.2
9.1
9.0
8.9
8.8
8.7
8.6
8.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
ppm
0.95
1.89
0.95
0.96

FIGURE – 35

^{13}C NMR SPECTRUM OF 3-ME-PYRIDO-[1,2-a] PYRIMIDIN-2-ONE



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PROCNO             1

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PULPROG      zgpg30
TD            32768
SOLVENT        CDCl3
NS              806
DS                4
SWH      29761.904 Hz
FIDRES    0.908261 Hz
AQ       0.5505524 sec
RG              203
DW          16.800 usec
DE            6.50 usec
TE           299.5 K
D1      2.00000000 sec
D11     0.03000000 sec
TD0               1

======== CHANNEL f1 ========
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PL1           0.00 dB
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SFO1    125.7703643 MHz

======== CHANNEL f2 ========
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NUC2             1H
PCPD2        80.00 usec
PL2           0.00 dB
PL12         17.50 dB
PL13         17.50 dB
PL2W     23.53637505 W
PL12W     0.41854253 W
PL13W     0.41854253 W
SFO2    500.1320005 MHz

F2 - Processing parameters
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SF      125.7577890 MHz
WDW              EM
SSB               0
LB             1.00 Hz
GB                0
PC             1.40
```
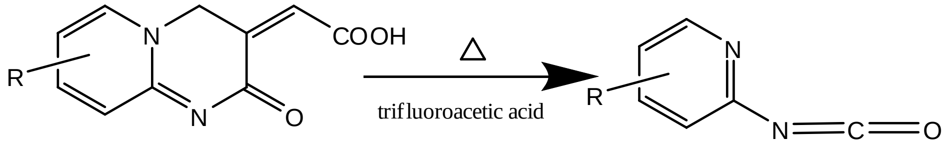

4.2.3. REACTION WITH TRI FLUORO ACETIC ACID

The reaction of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid **209** with trifluoro acetic acid under reflux in a steam bath yielded pure white crystals with pet ether.

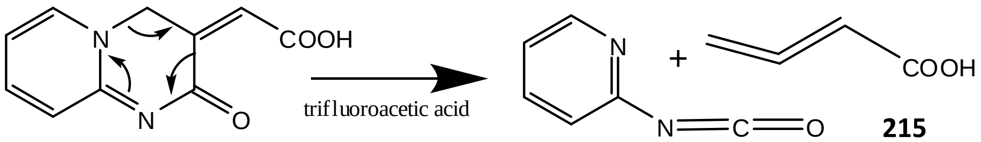


209 **214**

Scheme – 9

R = 3-Me, 4-Me, 5-Me

It was found that in this case also a rearrangement had taken place. The rearrangement was found to be Clasien like 3, 3 sigmatropic shift, with fragmentation of the pyrido nucleus affording 2-pyridyl isocyanate **214 [Scheme - 10].** Similar fragmentation with the formation of 2-pyridyl isocyanate was reported by **(Anne Fiksdahl et al, 2000)** in the flash vaccum thermolysis of pyridopyrimidinones.



214 **215**

Scheme – 10

The structure of the compound was confirmed by IR, ^{1}H **Figure -36** and ^{13}C NMR **Figure-37** analysis. IR showed a characteristic –CO stretching at 1687 cm^{-1}. ^{1}HNMR of the product **214** revealed signals at δ 7.5, 7.9, 6.7, 6.5 and 2.3 due to the pyridine nucleus and methyl at C_3. Further the ^{13}C spectrum showed seven carbon signals in accordance with the proposed structure. The C=O being shielded by the pi-electrons resonated up-field (δ 119). The other carbon signals were assigned based on HSQC spectrum. The other fragment **215** could not be isolated and therefore not identified. The ^{1}H and ^{13}C chemical shifts of the synthesized compounds **214a-214c** are presented in the **Tables-25 -27.**

TABLE – 25

NMR DATA OF 2-ISOCYANATO-3-METHYLPYRIDINE

^{1}H Chemical shift	2.2	7.5	6.7	7.8			
Hydrogen	H_3-Me	H_4	H_5	H_6			
^{13}C Chemical shift	156	129	140	113	139	17	119
Carbon	C_2	C_3	C_4	C_5	C_6	C_3-Me	-C=O

TABLE - 26

NMR DATA OF 2-ISOCYANATO-4-METHYLPYRIDINE

^{1}H Chemical shift	6.3	2.2	6.5	7.9			
Hydrogen	H_3	H_4-Me	H_5	H_6			
^{13}C Chemical shift	155	123	121	149	147	21	129
Carbon	C_2	C_3	C_4	C_5	C_6	C_4-Me	-C=O

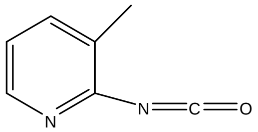
TABLE – 27

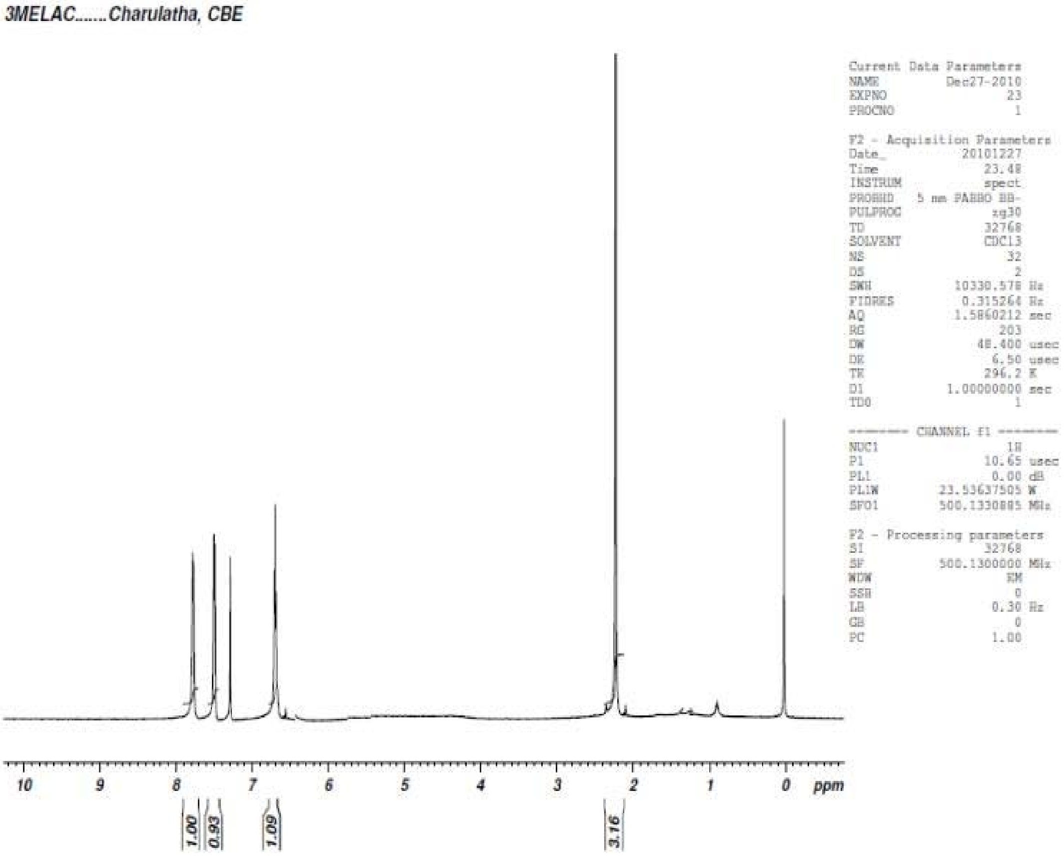
NMR DATA OF 2-ISOCYANATO-5-METHYLPYRIDINE

^{1}HChemical shift	7.3	6.4	2.2	7.8			
Hydrogen	H_3	H_4	H_5-Me	H_6			
^{13}C Chemical shift	147	109	136	139	156	17	123
Carbon	C_2	C_3	C_4	C_5	C_6	C_3-Me	-C=O

FIGURE – 36

^{1}H NMR SPECTRUM OF 2-ISOCYANATO-3-METHYLPYRIDINE





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TD                    32768
SOLVENT               CDCl3
NS                       32
DS                        2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ            1.5860212 sec
RG                      203
DW               48.400 usec
DE                 6.50 usec
TE                296.2 K
D1           1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                10.65 usec
PL1                0.00 dB
PL1W        23.53637505 W
SFO1        500.1330885 MHz

F2 - Processing parameters
SI                    32768
SF          500.1300000 MHz
WDW                      EM
SSB                       0
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PC                     1.00
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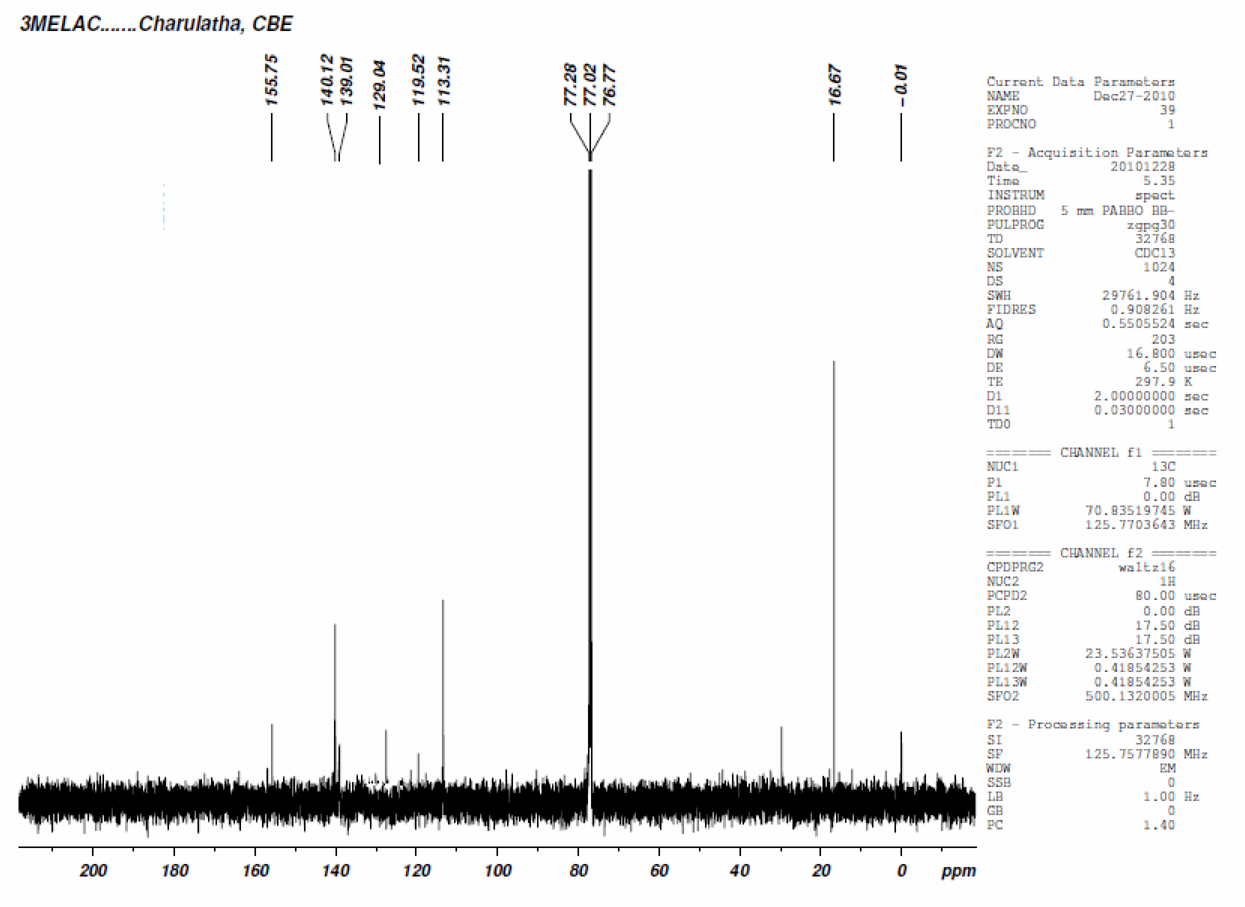
FIGURE – 37

^{13}C SPECTRUM OF 2-ISOCYANATO-3-METHYLPYRIDINE



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PULPROG          zgpg30
TD                 32768
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.50 usec
TE                 297.9 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======= CHANNEL f1 =======
NUC1                 13C
P1                  7.80 usec
PL1                 0.00 dB
PL1W         70.83519745 W
SFO1         125.7703643 MHz

======= CHANNEL f2 =======
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               17.50 dB
PL13               17.50 dB
PL2W         23.53637505 W
PL12W         0.41854253 W
PL13W         0.41854253 W
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

4.3 REDUCTION

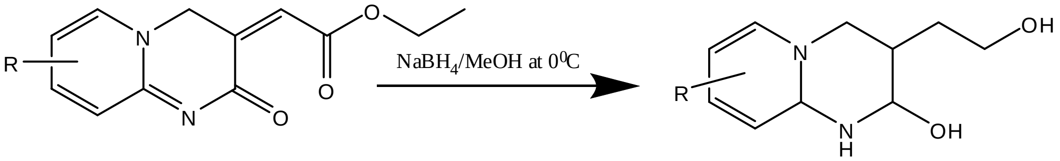
Reduction plays a very important role in organic synthesis. Conversion of aromatic carboxylic acids into their methyl esters and reduction to their corresponding alcohols is a key step in the synthesis of many natural products. Hence the behavior of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid in presence of two nucleophilic reducing agents viz, sodium borohydride and lithium aluminium hydride were studied.

4.3.1 Reduction with $NaBH_4$

$NaBH_4$ is a versatile reducing agent for the reduction of ketones, aldehydes and other functional groups. But it is not commonly used for the reduction of esters. However recently many reports have been published for the reduction of esters with sodium borohydride in MeOH **(Jorge et al, 2006)** or sodium borohydride in THF-MeOH **(Aamer Seed et al, 2006)** Hence it was anticipated to study the reduction of ethyl-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetate **216**, with sodium borohydride in methanol.

Reduction of ethyl-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene) acetates **216**, with sodium borohydride in methanol at 0^0C afforded 3-(2-hydroxyethyl)-2,3,4,9a-tetrhydro-1H-pyrido[1,2-a]pyrimidin-2-ols **217** with lower melting points and with low yields (28-32%). TLC showed four spots indicative of the presence of other minor by products. The compound was purified by column chromatography.

The structural assignment was made by ^{1}HNMR **Figure-38** ^{13}CNMR-**Figure-39** and IR spectroscopy. The IR spectrum of **217b** showed characteristic broad band from 2796 cm^{-1}- 3200 cm^{-1} and 1385 cm^{-1} indicating the presence of -NH and -OH group respectively. The absence of strong absorption band at 1680-1700 cm^{-1} revealed that reduction of –CO group might have occurred. Also the absence of absorption band at 1634 cm^{-1} suggested the reduction of C=N group. The ^{1}H NMR spectrum of the compound **217b** displayed 12 signals and ^{13}C displayed 10 carbon signals. Increased number of signals in aliphatic region suggested reduction of ester group as well as the exocyclic double bond while the appearance signals at δ 7.7, 7.5 and 6.7 indicated that the reduction pyridine nucleus had not occurred. A broad singlet at δ 1.7 confirmed the presence of –NH group. The mass spectrum showed M^+ peak at m/z 212 in accordance with the proposed structure. **Tables 29-32** – summarize the observed NMR data for the compounds **217b-e.**



216

Scheme - 11

217

R= (a) 3-Me, (b)4-Me (c)5-Me and (d)6-Me

Since the yield of the reaction was low and formation of the byproducts was high it was thought of carrying out the reaction in presence of micellar media to improve the yields and to reduce the formation of byproducts.

Self-organized aggregates such as aqueous micellar media can bind the otherwise insoluble organic substrates by incorporating their hydrophobic part in the micellar interior and exposing their polar part at the water-micelle interface. Moreover, they offer a clean and viable alternative to traditional methods of accomplishing organic transformation with the prospect of selection through use of appropriate surfactants. The intrinsic solubilisation ability of micelles provides a discrete reaction site at the micro heterogeneous interface by bringing the reacting molecules in close proximity. Hence the local interfacial concentrations of reactants get enhanced compared to their stoichiometric concentration. The energy of activation is lowered presumably due to increased collisions between such interfacially concentrated reactants **(Debapratim Das et al, 2004).** As expected the yield of the reaction increased **Table- 28.**

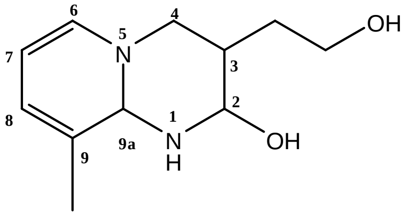
Table- 28

YIELD OF COMPOUNDS 217a-e

Compound	**Yield in %**	
	$NaBH_4$/MeOH at 0^0C	**$NaBH_4$/MeOH /SDS at 0^0C**
217a	28	36
217b	31	43
217c	31	44
217d	30	41
217e	31	42

TABLE -29

NMR DATA OF 3-(2-HYDROXYETHYL)-9 METHYL-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL



^{1}H Shift in ppm	1.2	1.6	2.0	2.1	2.3	3.5	3.7	4.5	6.4	6.7	7.3	7.5
Multiplicity/ no. of ^{1}H	m/2	m/1	q/2	s/3	b(s)/1	d/2	q/1	d/1	t/1	b(s)/2	s/1	q/1
Hydrogen	H_2	H_3	H_3'	H_3''	H_4	H_6	H_7	H_8	H_9-Me	H_{10}	-NH	OH
C^{13} shift in ppm	66	39	30	63	42	148	105	111	122	65	15	
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_{10}	C_9-Me	

TABLE -30

NMR DATA OF 3-(2-HYDROXYETHYL)-8-METHYL-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL

^{1}H Shift in ppm	4.2	2.0	1.3	3.6	2.4	7.5	5.8	2.1	4.9	1.6	5.3
Multiplicity/ no. of ^{1}H	m/2	q/2	m/2	q/2	d/2	q/1	m/1	s/3	q/1	b(s)/1	b(s)/2
Hydrogen	H_2 & H_{10}	H_3	H_3'	H_3''	H_4	H_6	H_7	H_8-Me	H_9	-NH	OH
C^{13} shift in ppm	66	37	30	63	53	143	109	112	122	64	17
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_{10}	C_8-Me

TABLE -31

NMR DATA OF 3-(2-HYDROXYETHYL)-7-METHYL-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL

^{1}H Shift in ppm	4.2	1.7	1.3	3.2	0.2	6.8	2.5	6.7	6.5	2.6	6.4
Multiplicity/ no. of ^{1}H	q/2	d/1	m/2	q/2	d/2	d/1	s/3	d/1	d/1	b(s)/1	b (s)/2
Hydrogen	H_2 & H_{10}	H_3	H_3'	H_3''	H_4	H_6	H_7-Me	H_8	H_9	-NH	OH
C^{13} shift in ppm	66	37	30	63	53	143	109	112	122	64	17
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_{10}	C_7-Me

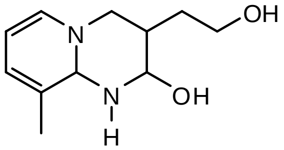
TABLE -32

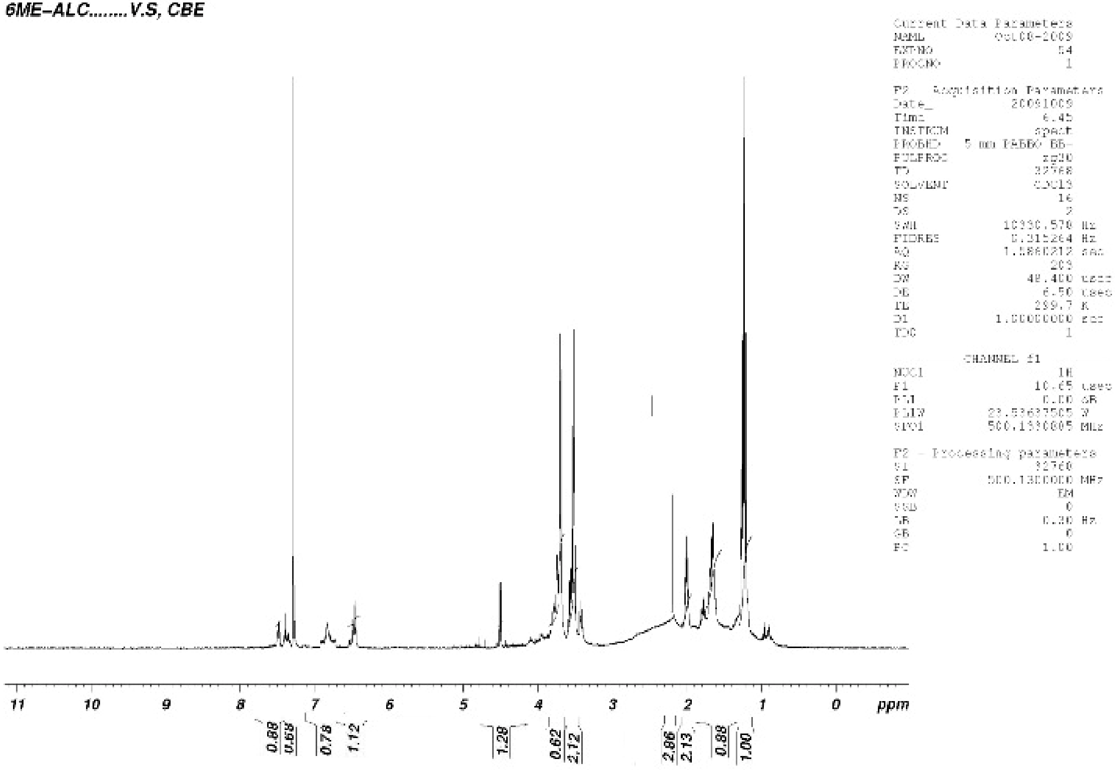
NMR DATA OF 3-(2-HYDROXYETHYL)-6-METHYL-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL

^{1}H Shift in ppm	3.6	1.4	0.9	3.3	2.3	7.7	6.8	7.5	1.3	4.2	1.7	6.0
Multiplicity/ no. of ^{1}H	s/1	t/1	m/2	d/2	d/2	q/1	d/1	q/1	s/3	m/1	b(s)/1	b(s)/2
Hydrogen	H_{3}'	H_{3}	H_{4}	H_{6}-Me	-NH	H_{3}''	H_{2}	H_{10}	H_{9}	OH	H_{7}	H_{8}
C^{13} shift in ppm	66	37	30	63	53	143	109	112	122	64	17	
Carbon	C_{2}	C_{3}	C_{3}'	C_{3}''	C_{4}	C_{6}	C_{7}	C_{8}	C_{9}	C_{10}	C_{6}-Me	

FIGURE – 38

^{1}H NMR SPECTRUM OF 9 METHYL-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL





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PROCNO                 1

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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ            1.5860212 sec
RG                   203
DW               48.400 usec
DE                 6.50 usec
TE                299.7 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
PL1                 0.00 dB
PL1W         23.53637505 W
SFO1         500.1330805 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```
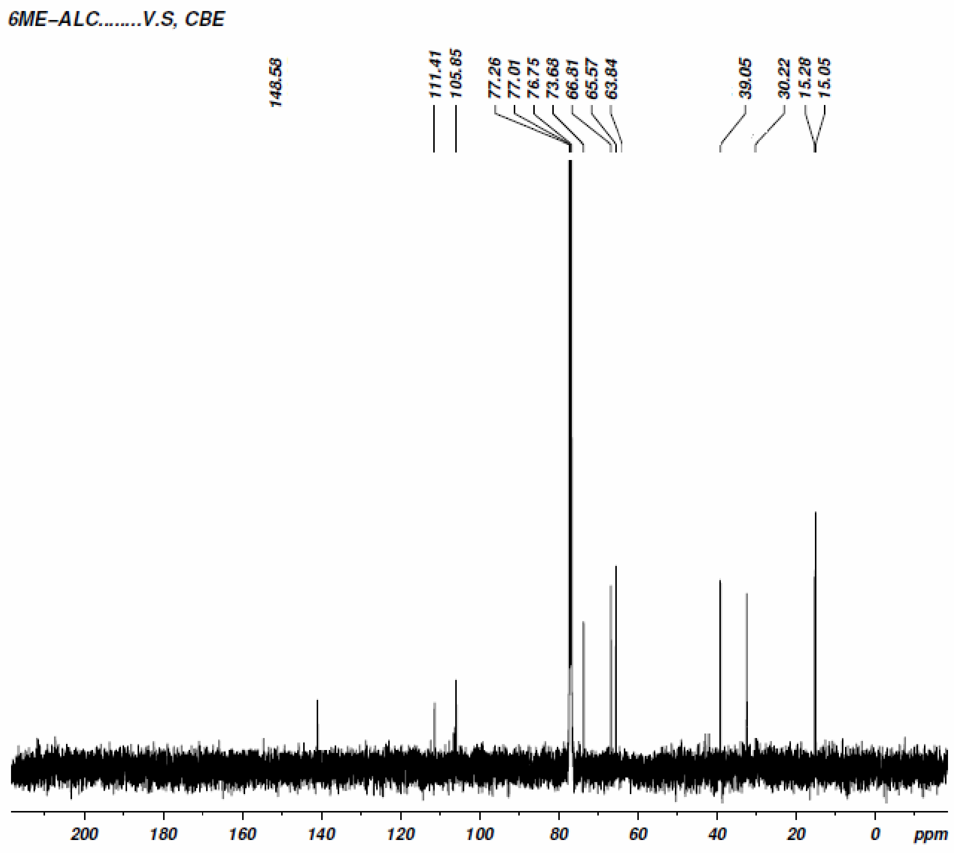

FIGURE – 39

^{13}C NMR SPECTRUM OF 9 METHYL-2,3,4,9a-TETRAHYDRO-1H-PYRIDO[1,2-a]PYRIMIDIN-2-OL



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PROCNO                   1

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INSTRUM              spect
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PULPROG            zgpg30
TD                   32768
SOLVENT              CDCl3
NS                    2000
DS                       4
SWH             29761.904 Hz
FIDRES           0.908261 Hz
AQ              0.5505524 sec
RG                     203
DW                  16.800 usec
DE                    6.50 usec
TE                   301.4 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

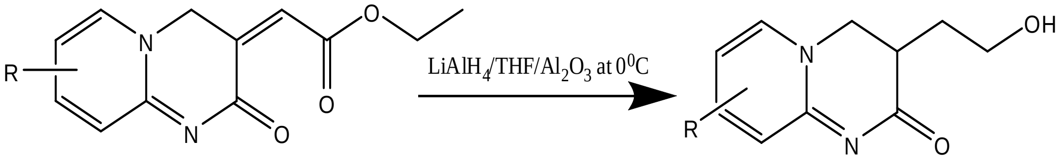
======== CHANNEL f1 ========
NUC1                   13C
P1                    7.80 usec
PL1                   0.00 dB
PL1W           70.83519745 W
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   0.00 dB
PL12                 17.50 dB
PL13                 17.50 dB
PL2W           23.53637505 W
PL12W           0.41854253 W
PL13W           0.41854253 W
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                   32768
SF             125.7577890 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

4.3.2 Reduction with $LiAlH_4$

The reduction of ethyl-2-(2-oxo-2Hpyrido[1,2-a]pyrimidin-3(4H)-ylidene) acetates **216** were also carried out in the presence of $LiAlH_4$/THF at 0^0C. The TLC showed too many spots. Even the major product could not be isolated. Hence the reaction was carried out in presence of activated alumina. The formation of byproducts was reduced in presence of activated alumina and the products were isolated with approximately 50-55% yield. The compounds were purified by coloumn chromatography and were characterized by IR, ^{1}HNMR **Figure-40** and ^{13}CNMR **Figure-41**. The IR spectrum registered characteristic band for –OH and –CO group at 3450cm^{-1} and 1687cm^{-1} respectively. The NMR spectrum for the compound **218b** displayed peaks at δ 3.2, 4.9, 7.6, 7.51, 6.7, 1.6, 4 and 2.3 respectively. ^{13}C NMR showed 10 signals. Also a signal at δ 177 observed in ^{13}C spectrum confirmed the presence of –CO group which was in accordance with the proposed structure. **Tables - 33-36** summarizes the observed NMR data for the compounds **218b-218e.**



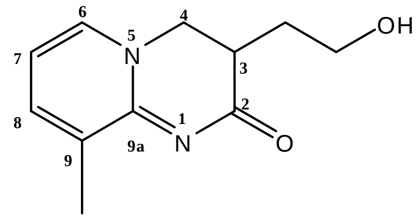
Scheme - 12

R= (a) 3-Me,(b)4-Me(c)5-Me & (d)6-Me

Since lithium aluminium hydride is a specific reagent for the reduction of ester group ,reduction of the –CO group was not observed as in the case of sodium borohydride which was a general reagent for reduction of aldehydes, ketones and other functional groups.

TABLE -33

NMR DATA OF 3-(2-HYDROXYETHYL)-9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE



^{1}H Shift in ppm	3.2	1.6	4.0		7.6	6.7	7.5	2.4	6.2		
Multiplicity/ no. of ^{1}H	q/1	q/2	t/2		s/1	d/1	d(d)/1	s/3	b(s)/1		
Hydrogen	H_3	H_3'	H_3''		H_6	H_7	H_8	H_9-Me	OH		
C^{13} shift in ppm	177	41	32	62	132	122	111	105	76	15	164
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_9-Me	C_{10}

TABLE -34

NMR DATA OF 3-(2-HYDROXYETHYL)-8-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	3.1	1.7	4.1		7.6	7.2	6.72	2.2	6.3		
Multiplicity/ no. of ^{1}H	q/1	q/2	t/2		s/1	d/1	(d)/1	s/3	b(s)/1		
Hydrogen	H_3	H_3'	H_3''		H_6	H_7	H_9	H_8-Me	OH		
C^{13} shift in ppm	177	41	32	62	132	122	111	105	76	15	164
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_9-Me	C_{10}

TABLE -35

NMR DATA OF 3-(2-HYDROXYETHYL)-7-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	3.2	1.6	4.0		7.7	6.7	7.4	2.2	6.2		
Multiplicity/ no. of ^{1}H	q/1	q/2	t/2		s/1	d/1	d(d)/1	s/3	b(s)/1		
Hydrogen	H_3	H_3'	H_3''		H_6	H_7	H_8	H_9-Me	OH		
C^{13} shift in ppm	177	41	32	62	132	122	111	105	76	15	164
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_9-Me	C_{10}

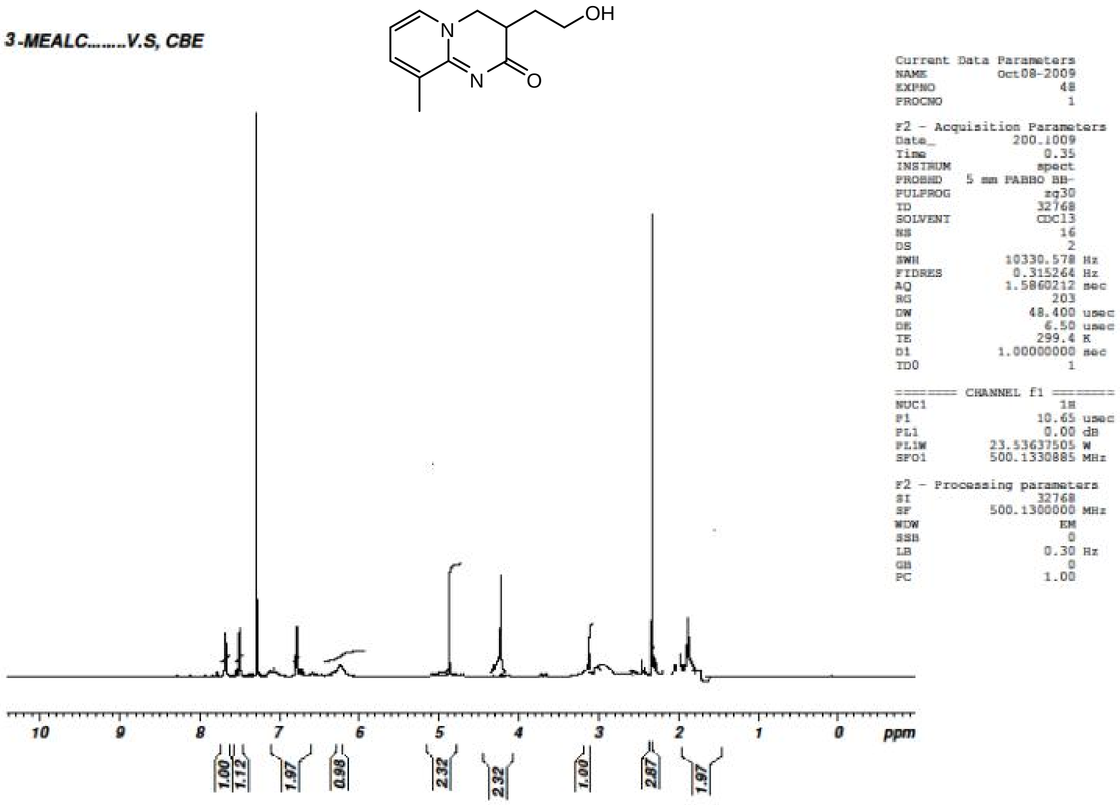
TABLE -36

NMR DATA OF 3-(2-HYDROXYETHYL)-6-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	3.1	1.6	4.1		2.1	7.2	7.6	6.8	6.0		
Multiplicity/ no. of ^{1}H	q/1	q/2	t/2		s/3	d/1	s/1	(d)/1	b(s)/1		
Hydrogen	H_3	H_3'	H_3''		H_6-Me	H_7	H_8	H_9	OH		
C^{13} shift in ppm	177	41	32	62	132	122	111	105	76	15	164
Carbon	C_2	C_3	C_3'	C_3''	C_4	C_6	C_7	C_8	C_9	C_9-Me	C_{10}

FIGURE – 40

^{1}HNMR SPECTRUM OF9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE



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PROCNO                   1

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PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              10330.578 Hz
FIDRES            0.315264 Hz
AQ               1.5860212 sec
RG                     203
DW                  48.400 usec
DE                    6.50 usec
TE                   299.4 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.65 usec
PL1                   0.00 dB
PL1W           23.53637505 W
SFO1           500.1330885 MHz

F2 - Processing parameters
SI                   32768
SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```
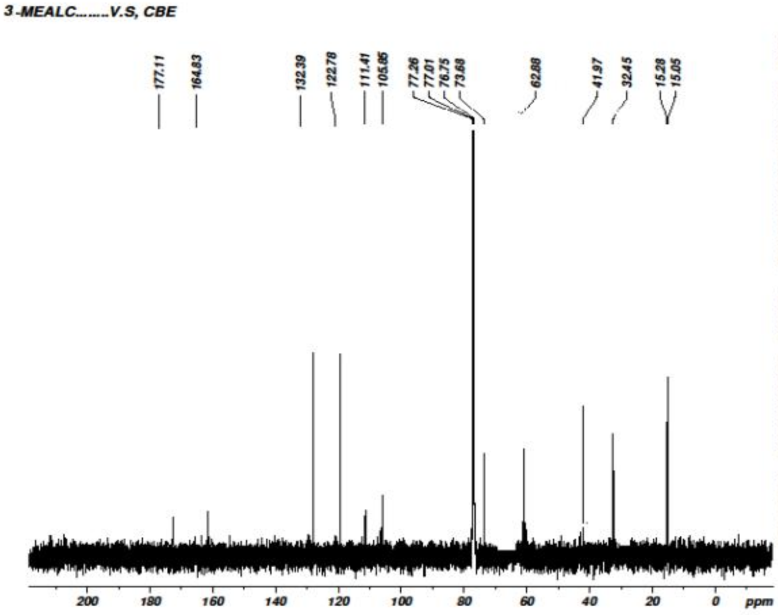

FIGURE – 41

^{13}CNMR SPECTRUM OF 9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE



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Current Data Parameters
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EXPNO                 55
PROCNO                 1

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Time                8.13
INSTRUM            spect
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PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                  2000
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.50 usec
TE                 301.4 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

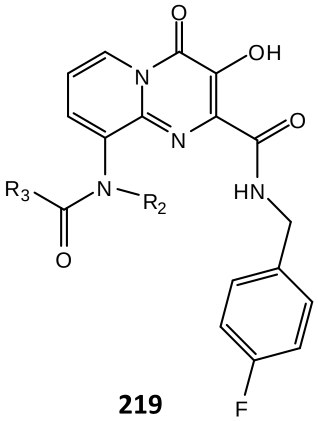
======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
PL1                 0.00 dB
PL1W         70.83519745 W
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               17.50 dB
PL13               17.50 dB
PL2W         23.53637505 W
PL12W         0.41854253 W
PL13W         0.41854253 W
SFO2         500.1320005 MHz

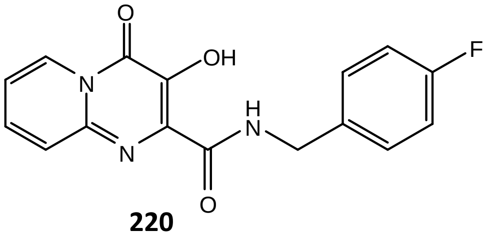
F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

4.4. SYNTHESIS OF 2-OXO-2H-PYRIDO[1,2-A]PYRIMIDIN-3(4H)-YLIDENE)-N-PHENYLACETAMIDES

3-hydroxy-4-oxo-4H pyrido[1,2-a] pyrimidine-2-carboxylates **219** and **220** were found to be potent inhibitor for HIV-1 virus **(Monica donghi et al, 2009 and Olaf Kinzel et al, 2008)**



219

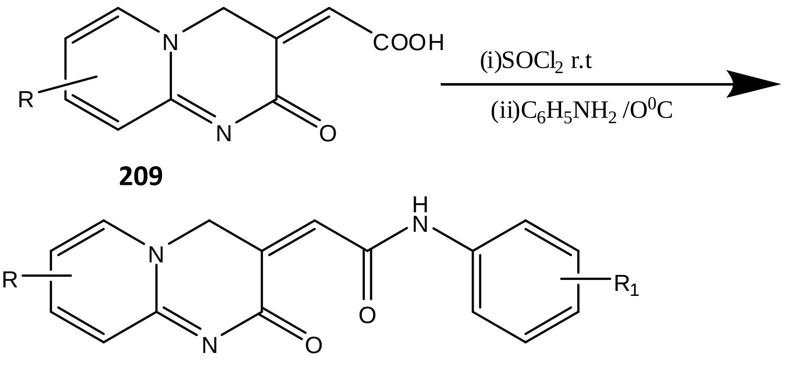


220

With this in mind synthesis of series of N-aryl amides of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acids were carried out. The amides were prepared in two steps viz

(i) Conversion of acid to acid chloride using thionyl chloride

(ii) Treatment of acid chloride with various amines to afford N-arylamides with moderate yields.



221

Scheme -13

R= H, 3-Me & 5-Me; R$_1$ =aniline, p-toludine, p-chloroaniline, p-anisidine, 2,3-dimethoxy aniline & benzyl amine

The synthesized compounds **221a-f** were characterized by IR, ^{1}H and ^{13}C NMR spectral measurements. IR displayed characteristic -NH band at 3243 cm^{-1} and at 1734 cm^{-1}, 1630 cm-^{1} for the two carbonyls. The ^{1}H NMR of the spectrum of the compound **221a Figure-42** exhibited peaks at δ 4.5 and 6.3 corresponding to H_4 and H_3' respectively. A multiplet at δ 7.0 - 8 were due to the pyridine and benzene nucleus of amine fragment. ^{13}C registered 16 signals (**Figure-43**) and mass spectrum displayed M$^+$ peak at m/z =280 (**Figure-44)** confirming the suggested structure. The ^{1}H NMR values for the compounds **221 b-f** are given in the following **Tables 37-41.**

TABLE -37

^{1}HNMR DATA OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)-N-P-TOLYLACETAMIDE

^{1}H Shift in ppm	6.8	4.5	7-8	9.1	2.0
Multiplicity/ no. of ^{1}H	d/1	s/2	m/8	s(b)/1	s/3
Hydrogen	H_3'	H_4	Aromatic + pyridine ring	-NH	-CH_3

TABLE -38

^{1}HNMR DATA OF N-(4-CHLOROPHENYL)-2-(2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETAMIDE

^{1}H Shift in ppm	6.8	4.6	7-8	9.0
Multiplicity/ no. of ^{1}H	d/1	s/2	m/8	s(b)/1
Hydrogen	H_3'	H_4	Aromatic + pyridine ring	-NH

TABLE -39

^{1}HNMR DATA OF N-(4-METHOXYPHENYL)-2-(2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETAMIDE

^{1}H Shift in ppm	6.5	4.2	7-8	9.2	3.8
Multiplicity/ no. of ^{1}H	d/1	s/2	m/8	s(b)/1	s/3
Hydrogen	H_3'	H_4	Aromatic + pyridine ring	-NH	$-OCH_3$

TABLE -40

^{1}HNMR DATA OF N-(2,5-DIMETHOXYPHENYL)-2-(2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETAMIDE

^{1}H Shift in ppm	6.8	5.1	7-8	9.3	3.8	3.9
Multiplicity/ no. of ^{1}H	d/1	s/2	m/7	s(b)/1	s/3	s/3
Hydrogen	H_3'	H_4	Aromatic + pyridine ring	-NH	$-OCH_3$	$-OCH_3$

TABLE -41

^{1}HNMR DATA OF N-BENZYL-2-(2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETAMIDE

^{1}H Shift in ppm	6.8	4.5	3.3	7-8	9.0
Multiplicity/ no. of ^{1}H	d/1	s/2	s/2	m/8	s(b)/1
Hydrogen	H_3'	H_4	$-CH_2$	Aromatic + pyridine ring	-NH

FIGURE – 42

^{1}H NMR SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE) ACETAMIDE

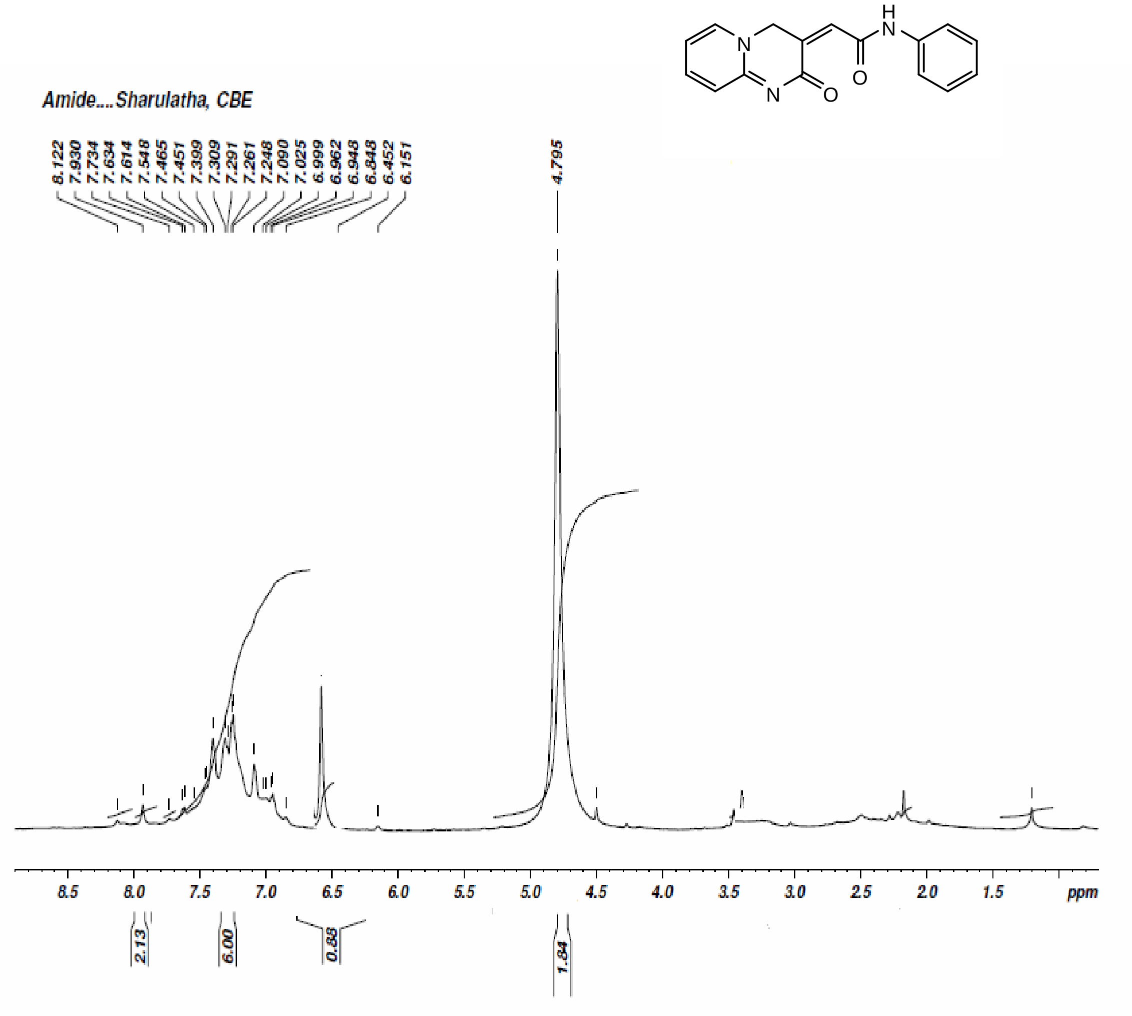


FIGURE – 43

^{13}C NMR SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)-ACETAMIDE

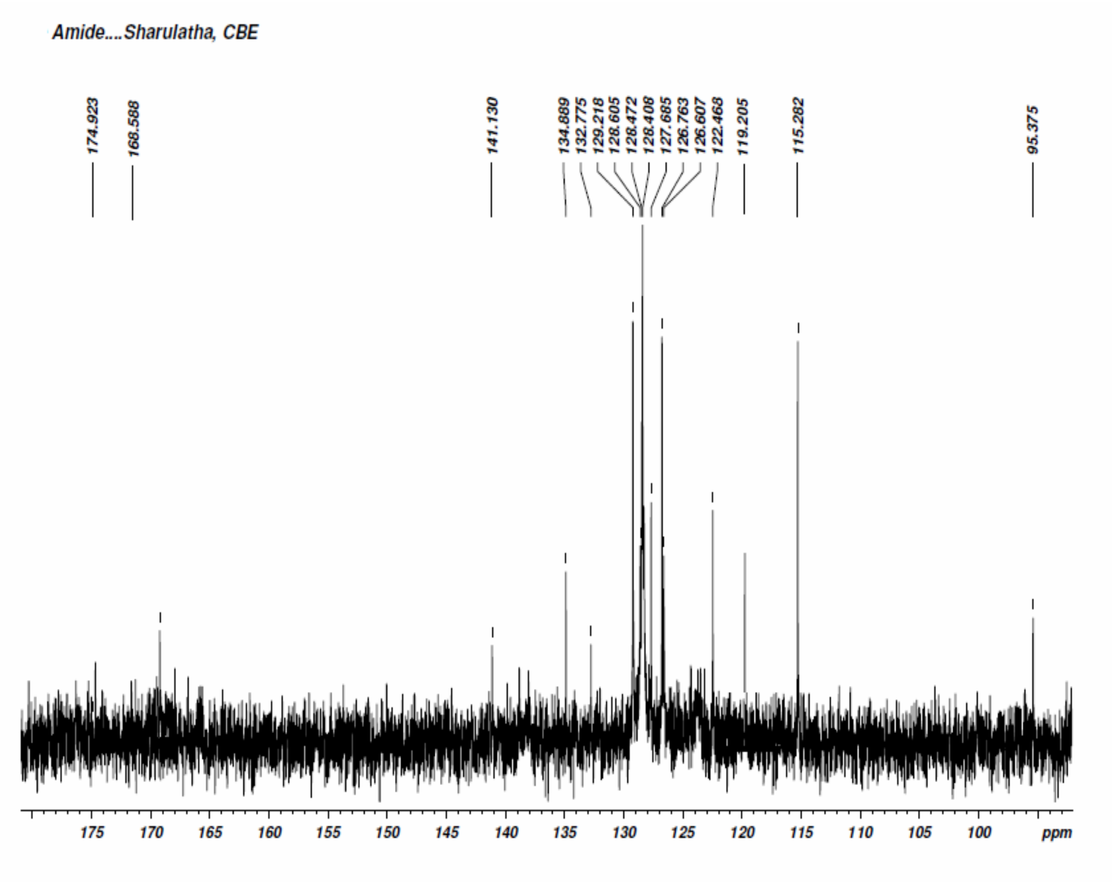
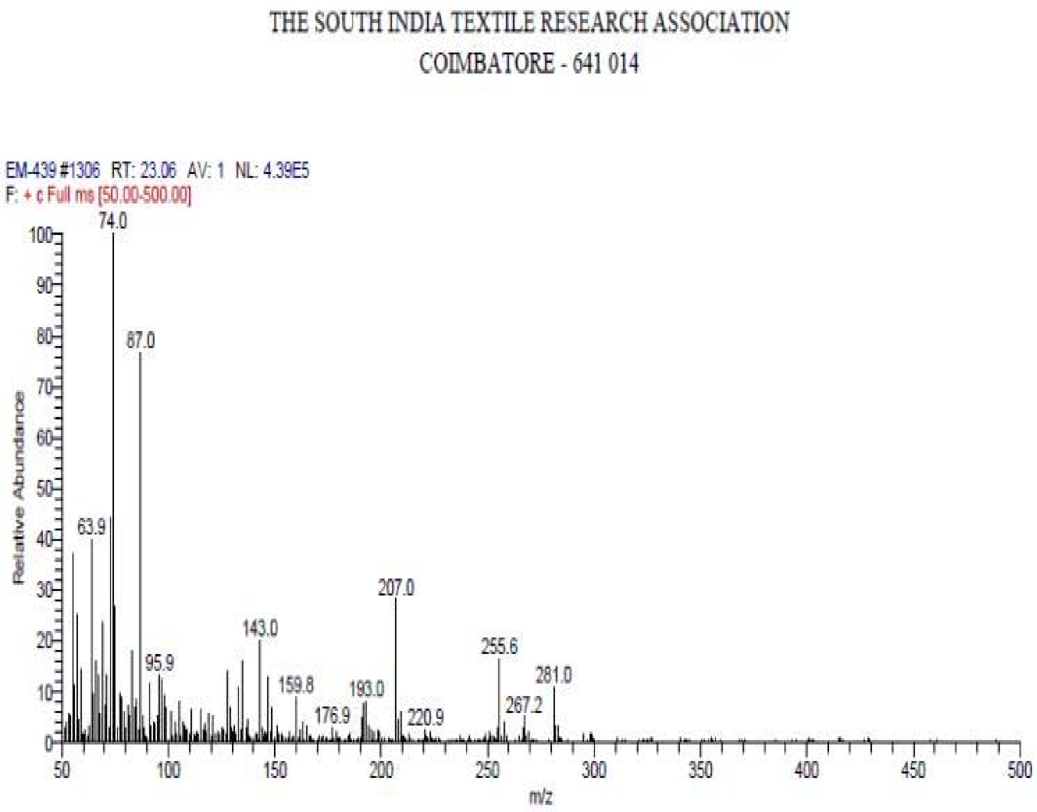


FIGURE – 44

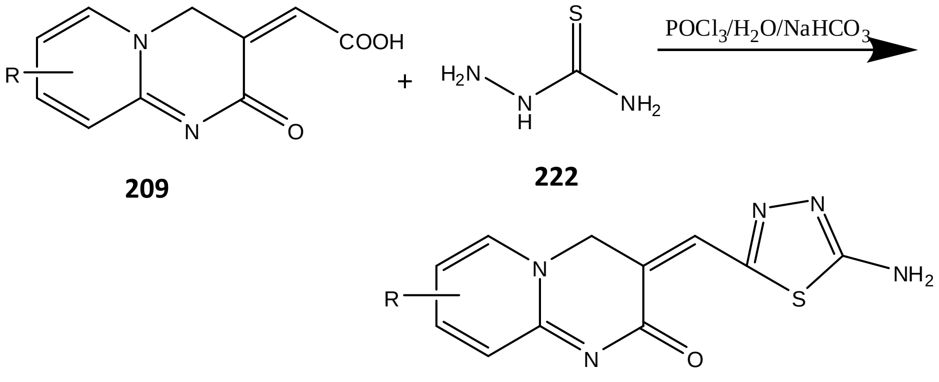
MASS SPECTRUM OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETAMIDE



4.5. SYNTHESIS OF (5- AMINO 1,3,4 THIA DIAZOL-2YL) -3,4 –DIHYDRO-2H –PYRIDO[1,2-a]PYRIMIDIN-2-ONES

The synthesis of compounds incorporating 1,3,4 thia diazole ring have attracted wide spread attention due to their diverse pharmacological properties such as antimicrobial, anti-inflammatory analgesic and anti tumoral activities. Several 1,3,4 thiadiazole have been found to be biologically active e.g they showed the anticancer, antiviral anti-inflammatory and anticonvulsant activity **(Jumat Salimon et al, 2010).** Hence it was thought to incorporate 1,3,4 thia diazole moiety into the pyrido[1,2-a] pyrimidone nucleus.

The compounds 5-amino-(1,3,4-thia diazol-2yl)-3,4-dihydro-2H-pyrido [1,2-a]pyrimidine-2-ones were prepared by the reaction of the 2-oxo-2H pyrido[1,2-a]-pyrimidin-ylidine-2-one acetic acid with thio-semicarbazide in $POCl_3$, followed by the neutralization with sodium bicarbonate in good yields.



209

222

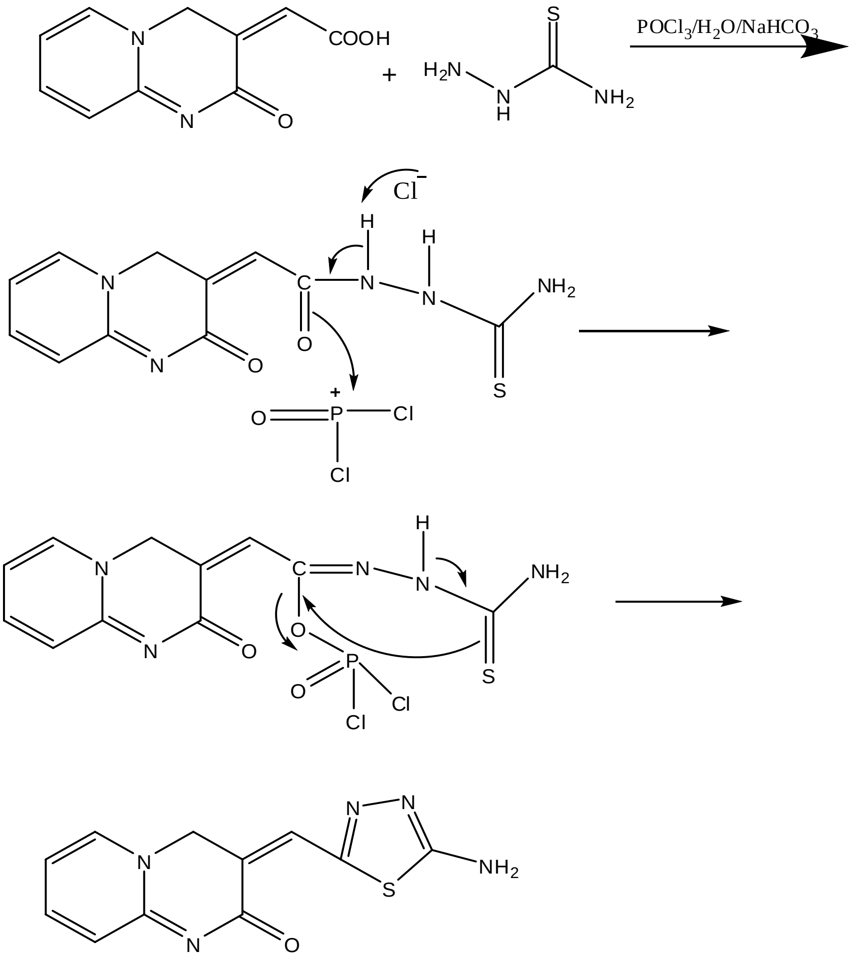
223

Scheme –14

R= H, 3-Me,4-Me,5-Me,6-Me

Evidence for the synthesized compounds **223a-e** were obtained from IR, ^{1}HNMR ^{13}CNMR and mass spectral analysis. In the IR spectra of the compound **223a** a strong broad absorption band around 3290-3100 cm-1 was observed due to the $–NH_2$ stretching vibrations. The bands at 1615 cm^{-1} and 1499 cm^{-1} were attributed to the presence of –C=O and –C=N group respectively in the product. The ^{1}HNMR **Figure-45** spectra showed all the characteristic signals, for the pyrido pyrimidine nucleus at δ 7.0, 7.2, 7.7, 8.2, 8.3 and 5.0 for the compound **223a** ^{13}C NMR registered signals for all the carbon atoms **Figure-46** and in the mass M$^+$ was seen at m/z=270, **Figure-47** all in accordance with the suggested structure for the synthesized compound. The ^{1}H NMR and ^{13}C NMR values for the compounds **223 b-f** are given in the following **Tables 42-45.**

The formation of the product is represented in the scheme –15



Scheme –15

TABLE - 42

NMR DATA OF 3-((5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE)-9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^1H Shift in ppm	Multip-licity/no. of ^1H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
7.0	s/1	H_3'	177	C_2	122	C_8
5.5	s/2	H_4	138	C_3	143	C_9
8.5	d/1	H_6	120	C_3'	15	C_9-Me
6.9	d/2	H_7	95	C_3''	153	C_{10}
7.8	t/1	H_8	73	C_4	168	C-NH_2
2.2	s/3	H_9-Me	132	C_6		
5.1	b(s)2	-NH_2	113	C_7		

TABLE-43

NMR DATA OF 3-(5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE-8-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^1H Shift in ppm	Multip-licity/no. of ^1H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
7.2	s/1	H_3'	177	C_2	15	C_7-Me
5.0	s/2	H_4	138	C_3	143	C_8
8.0	d/1	H_6	120	C_3'	113	C_9
7.6	t/1	H_7	95	C_3''	153	C_{10}
2.2	s/3	H_8-Me	73	C_4	168	C-NH_2
6.9	d/2	H_9	132	C_6		
5.2	b(s)2	-NH_2	122	C_7		

TABLE-44

NMR DATA OF 3-(5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE-7-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
7.0	s/1	H_3'	177	C_2	15	C_7-Me
5.3	d/2	H_4	138	C_3	143	C_8
7.6	s/1	H_6	120	C_3'	113	C_9
2.2	s/3	H_7-Me	95	C_3''	153	C_{10}
7.8	d(d)/1	H_8	73	C_4	168	C-NH_2
6.9	d/1	H_9	132	C_6		
5.1	b(s)2	-NH_2	122	C_7		

TABLE-45

NMR DATA OF 3-(5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE-6-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

^{1}H Shift in ppm	Multiplicity /no. of ^{1}H	Hydrogen	C^{13} shift in ppm	Carbon	C^{13} shift in ppm	Carbon
7.2	t/1	H_3'	177	C_2	15	C_6-Me
5.1	s/2	H_4	138	C_3	143	C_8
2.3	s/3	H_6-Me	120	C_3'	113	C_9
7.6	d/1	H_7	95	C_3''	153	C_{10}
7.7	d/1	H_8	73	C_4	168	C-NH_2
6.8	t/2	H_9	132	C_6		
5.3	b(s)2	-NH_2	122	C_7		

FIGURE – 45

^{1}H NMR SPECTRUM OF 3-((5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE)-9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE

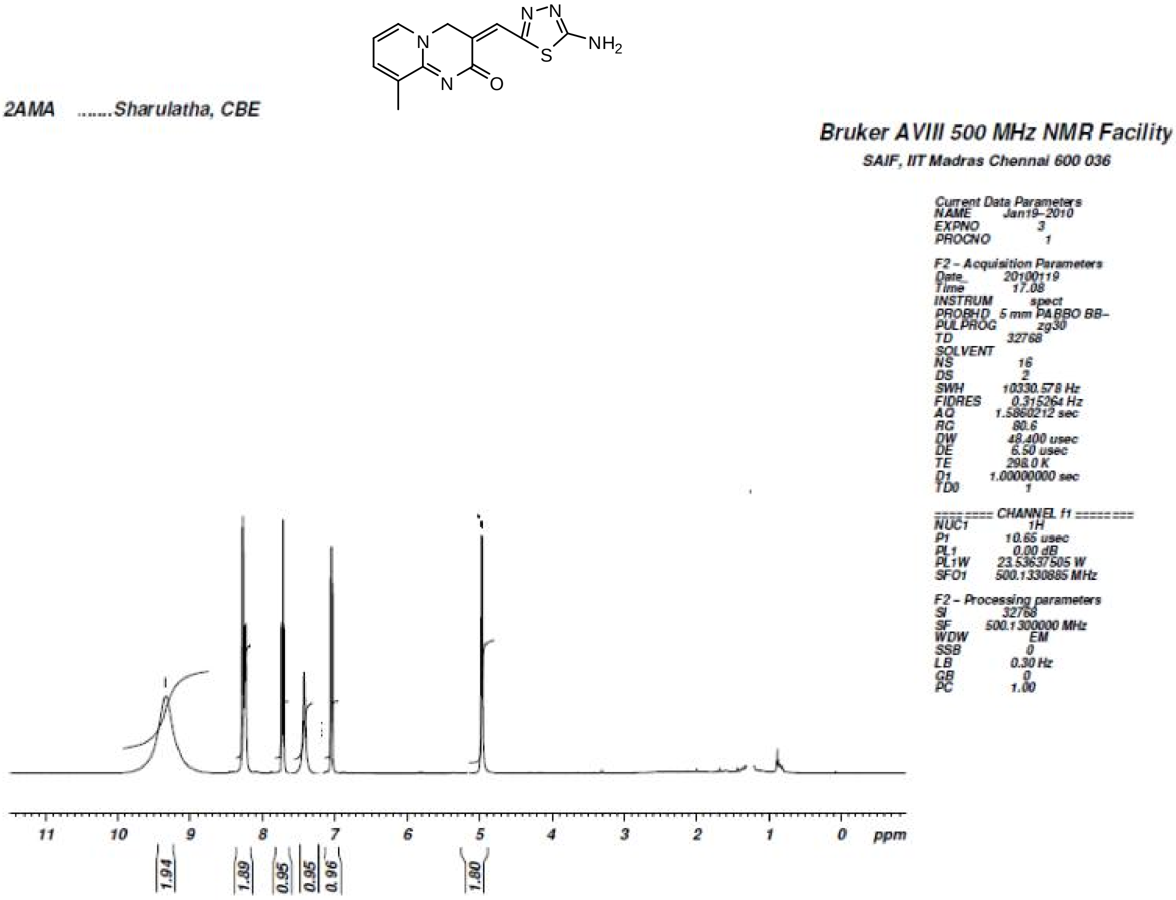
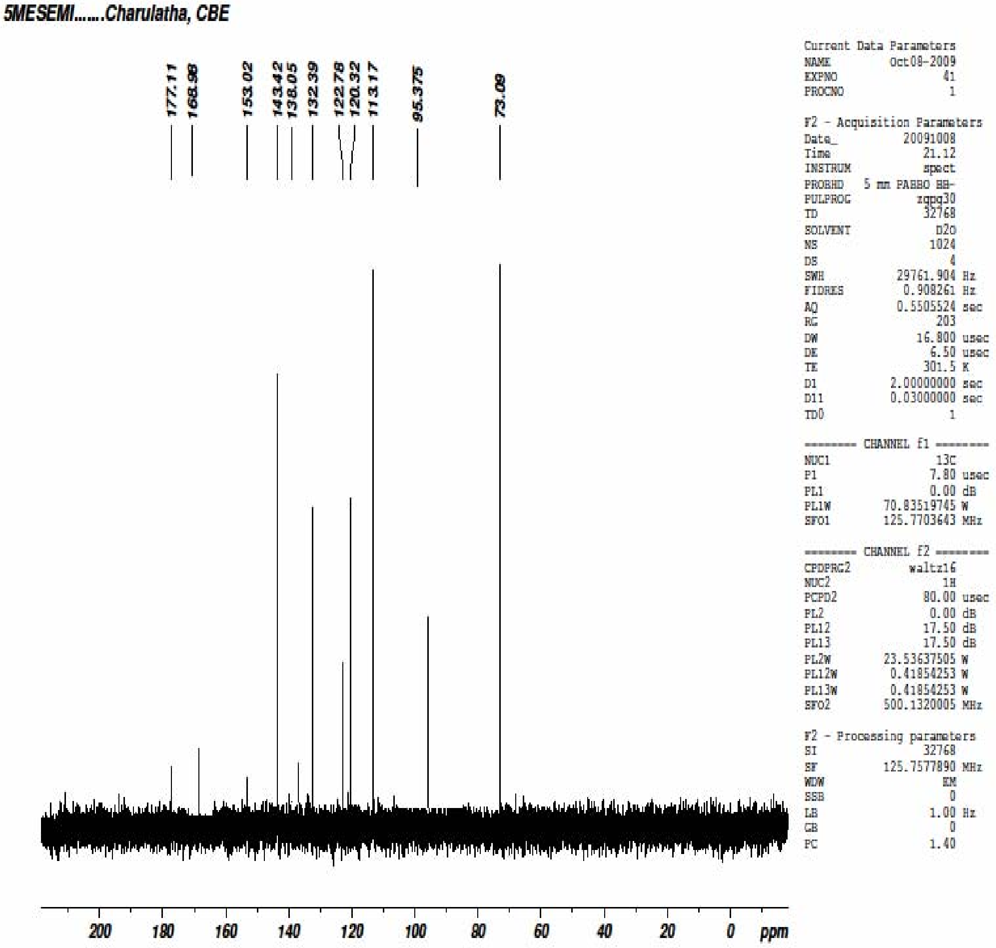


FIGURE – 46

^{13}C NMR SPECTRUM OF 3-((5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE)-9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE



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PULPROG          zgpg30
TD                 32768
SOLVENT              D2O
NS                  1024
DS                     4
SWH            29761.904 Hz
FIDRES          0.908261 Hz
AQ             0.5505524 sec
RG                   203
DW                16.800 usec
DE                  6.50 usec
TE                 301.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  7.80 usec
PL1                 0.00 dB
PL1W         70.83519745 W
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.00 dB
PL12               17.50 dB
PL13               17.50 dB
PL2W         23.53637505 W
PL12W         0.41854253 W
PL13W         0.41854253 W
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```
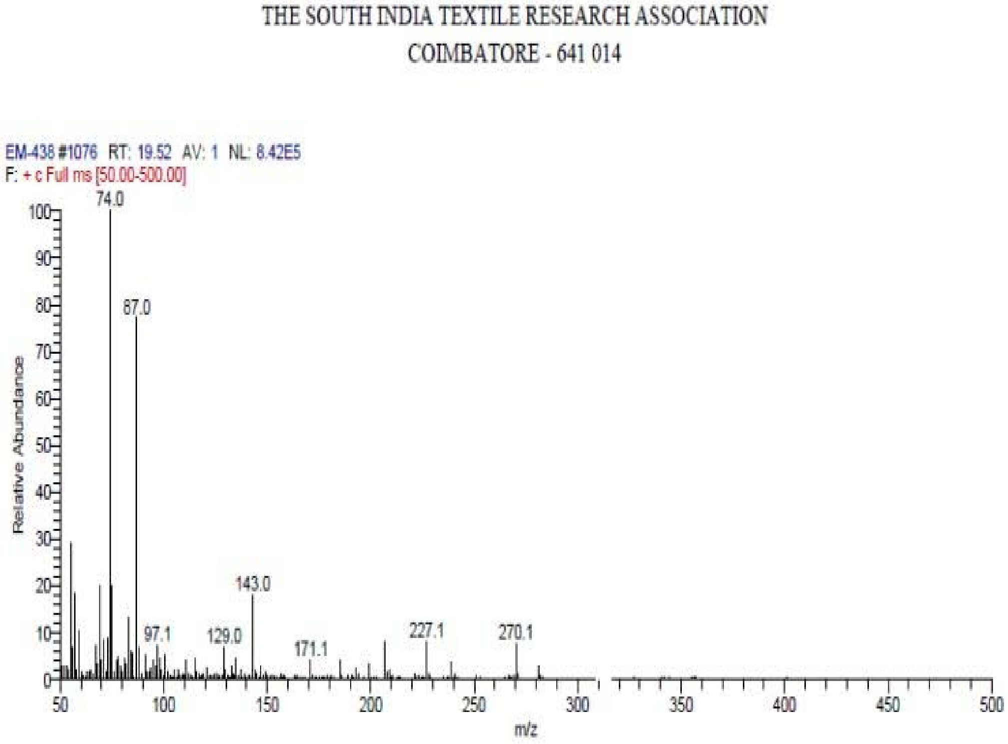

FIGURE – 47

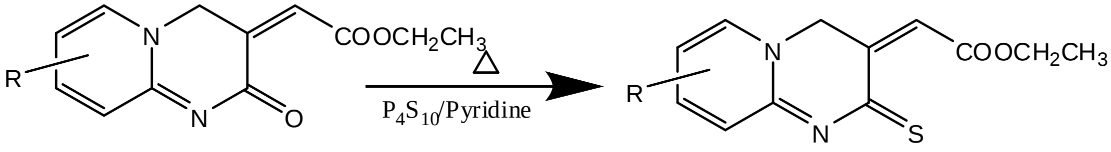
MASS SPECTRUM OF 3-((5-AMINO-1,3,4-THIADIAZOL-2-YL)METHYLENE)-9-METHYL-3,4-DIHYDRO-2H-PYRIDO[1,2-a]PYRIMIDIN-2-ONE



4.6. SYNTHESIS OF SULPHUR ANALOGUES OF 2-OXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ACETIC ACID

4.6.1. Synthesis of Ethyl 2-(2-thioxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene) acetates

Syntheses of organic compounds having a sulfur heteroatom have been in the interest of many groups. P_4S_{10} is a commercially available reagent which has been widely employed for the conversion of carbonyl to thiocarbonyl compounds. The thiocarbonyl compounds are important functional groups to perform various organic reactions or for use as end products in material and medicinal chemistry. Hence an attempt was made to transform the carbonyl group in 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acids **209** to thio carbonyl group.



216

224

Scheme –16

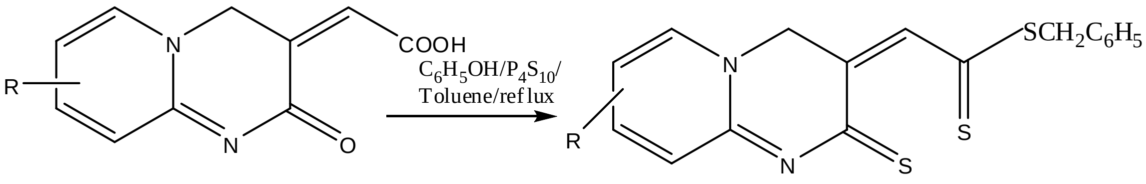
R= 3-Me, 4-Me, 5-Me

The esters of 2-oxo-2H-pyrido [1,2-a]pyrimidin-3(4H)-ylidene acetic acids **216** were refluxed with P_4S_{10} in presence of pyridine. The characterization of the compounds was done by IR, and ^{1}HNMR. In IR an absorption band at 1190cm^{-1} was observed which was characteristic for –C=S group. ^{1}HNMR of **224** displayed eight set of proton signals viz δ 1.4, 2.3, 4.2, 4.8, 6.2, 7.2, 7.5 and 8.1 for the compound **224a**. The signals at δ 6.2, 7.2, 7.5 and 8.1 were due to the pyrido pyrimdine ring nucleus, while the protons resonating at δ 1.4, 4.2 were attributed to the $–CH_3$ and $-CH_2$ of the ester group respectively.

4.6.2 Synthesis of Phenyl-2-(2-thioxo-2H-pyrido[1,2-apyrimidin-3(4H)-ylidene)ethanedithioate

Esters of dithiocarboxylic acids were versatile synthons in organic synthesis (**Metzer 1992**), valuable sensitizers in the manufacture of dyes and photographic materials **(Edward et al, 1951)**, potent agents in bactericidal, fungicidal and antitumor activities **(Christensen Ratclife et al, 1975).** So a trial was carried out to introduce dithiol ester group into the pyridopyrimidine nucleus which may be helpful to increase the biological properties of the 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acids.

Arumugam Sudalai et al, 2000 The 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acids were treated with P_4S_{10} in presence of benzyl alcohol in toluene. The dithiol esters were obtained in moderate yields.



209 **225**

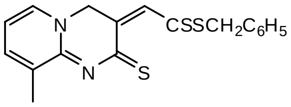
Scheme –17

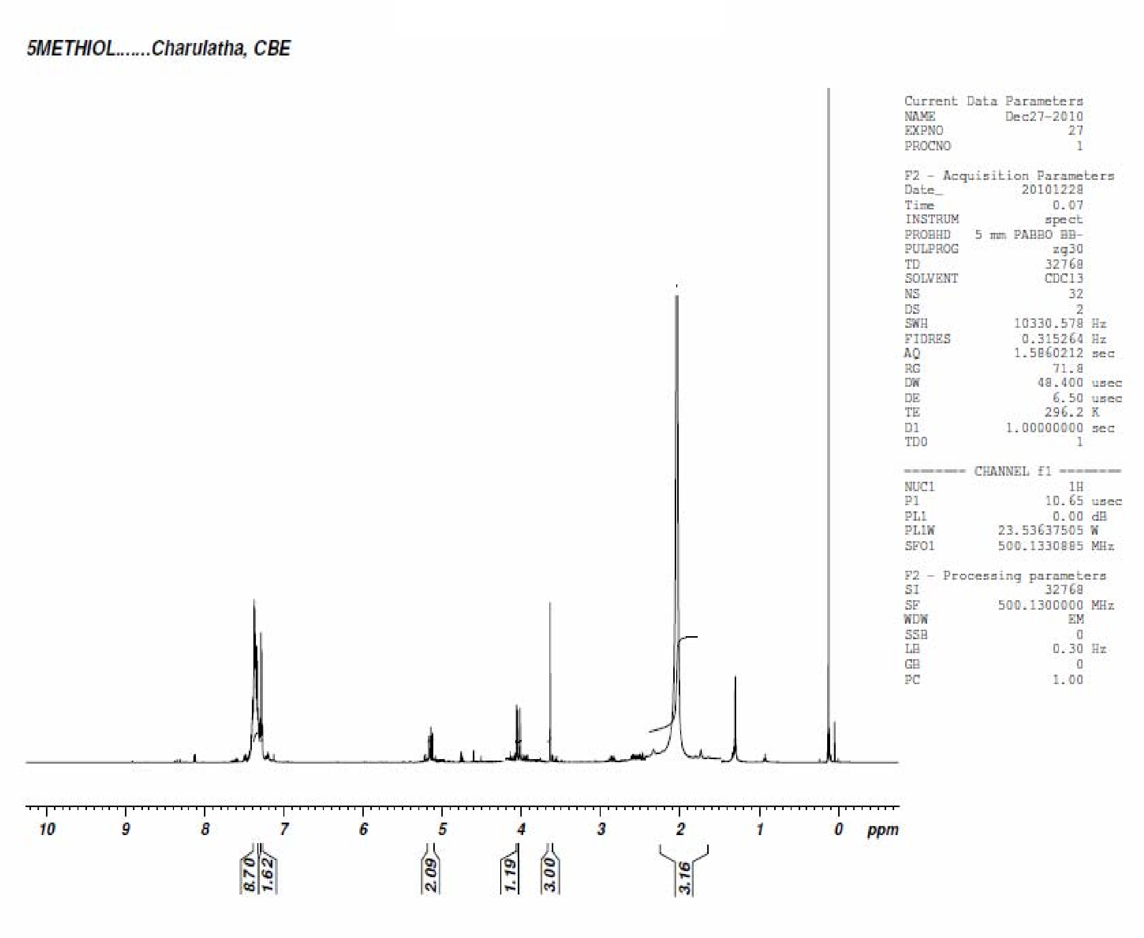
R= H ,3- Me,4-Me, 5-Me

The formation of dithiol ester is evidenced by the presence of two absorption bands at 1243 cm^{-1} and 1170 cm^{-1} attributing to the presence of two –C=S group. The ^{1}HNMR **Figure-48** of the compound **225b** displayed five sets of signals corresponding to the proposed structure. A multiplet around δ 7-8 was due to the pyridine ring and benzene nucleus. C_4 methylene appeared at δ 5.1 and the $–CH_2$ of aromatic nucleus appeared at δ 4.2. The ^{13}C **Figure-49** displayed 18 signals according to the proposed structure. The signals at δ 201 and δ 221 were due to the two –C=S groups which confirms the formation of dithiol ester.

FIGURE – 48

^{1}H NMR SPECTRUM OF PHENYL-2-(2-THIOXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ETHANEDITHIOATE





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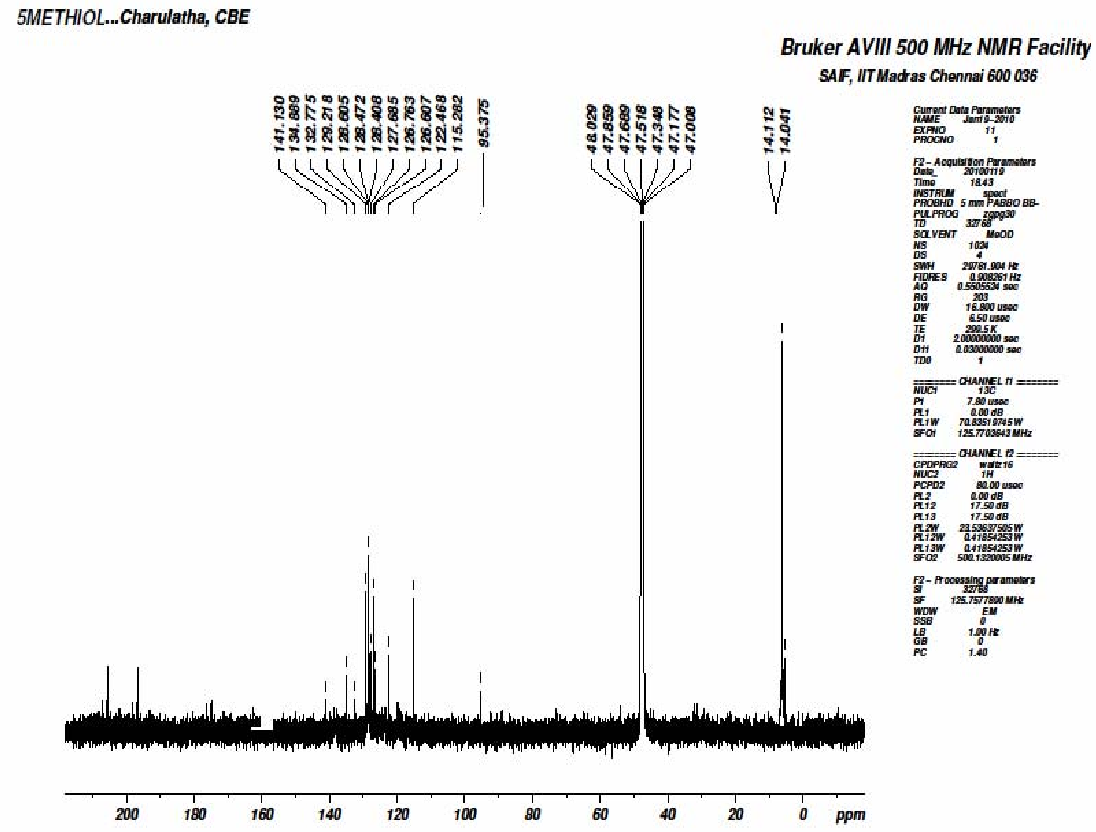
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     2
SWH           10330.578 Hz
FIDRES         0.315264 Hz
AQ            1.5860212 sec
RG                  71.8
DW                48.400 usec
DE                  6.50 usec
TE                 296.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.65 usec
PL1                 0.00 dB
PL1W         23.53637505 W
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

FIGURE – 49

^{13}C NMR SPECTRUM OF PHENYL-2-(2-THIOXO-2H-PYRIDO[1,2-a]PYRIMIDIN-3(4H)-YLIDENE)ETHANEDITHIOATE



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PROCNO            1

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PULPROG      zgpg30
TD            32768
SOLVENT        MeOD
NS             1024
DS                4
SWH      29761.904 Hz
FIDRES    0.908261 Hz
AQ       0.5505524 sec
RG              203
DW        16.800 usec
DE          6.50 usec
TE          299.5 K
D1      2.00000000 sec
D11     0.03000000 sec
TD0               1

======== CHANNEL f1 ========
NUC1            13C
P1          7.80 usec
PL1          0.00 dB
PL1W    70.83519745 W
SFO1   125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2      waltz16
NUC2              1H
PCPD2       80.00 usec
PL2          0.00 dB
PL12        17.50 dB
PL13        17.50 dB
PL2W    23.53637505 W
PL12W    0.41854253 W
PL13W    0.41854253 W
SFO2   500.1320005 MHz

F2 - Processing parameters
SI            32768
SF     125.7577890 MHz
WDW              EM
SSB               0
LB          1.00 Hz
GB                0
PC             1.40
```

4.7. BIOLOGICAL ACTIVITY

4.7.1. THEORETICAL PREDICTION OF BIOLOGICAL ACTIVITY

To predict the biological effects of the synthesized compounds the computational programmes OSIRIS, Chemdraw and Molinspiration softwares were used.

The compounds showed a positive value for drug likeliness as calculated from OSIRIS molecular property explorer. Also except in the case of **221b** and **221d** the compounds showed low risk against mutagenicity.

ClogP is the calculated log octanol/water partition coefficient, which is a measure for the lipophilicity of a compound. The logP is an important physicochemical parameter for oral absorption, since it relates to solubility and influences the ability of a compound to permeate through cell membranes including those of the intestinal epithelial cells. Too hydrophilic compounds (negative logP) are not able to pass through membranes, as they hardly enter the hydrophobic interior (mimicked by the octanol phase in the octanol/water system) of the lipophilic bilayer. Too lipophilic compounds (high logP) tend to be insoluble and also poorly permeate through membranes, as they get stuck in the lipophilic bilayer. Except for a few compounds **209a and 209e** other compounds show a low value for logP thus indicating the greater ability to penetrate through the membrane.

TABLE- 46

COMPUTED LOGP AND DRUG LIKELINESS PROPERTY

Compound	Chem draw		Molinspi-ration	OSIRIS				
	ClogP	tPSA	milogP	ClogP	Solubility	Drug likeliness	Drug score	Mutagen-city
209a	-0.078	69.97	0.3	-0.73	-0.84	4.54	0.97	Low risk
209b	0.322	69.97	0.65	-0.34	-0.96	4.35	0.97	Low risk
209c	0.322	69.97	0.48	-0.34	-0.96	4.41	0.97	Low risk
209d	0.644	69.97	0.48	-0.34	-0.96	4.91	0.97	Low risk
209e	0.079	69.97	-0.07	0.05	-1.09	4.92	0.97	Low risk
209f	0.866	69.97	0.1	0.44	-1.2	4.95	0.96	Low risk
209g	1.005	69.97	0.44	-0.27	-1.67	-0.97	0.6	Low risk
209h	1.382	69.97	0.79	0.12	-1.79	-1.26	0.59	Low risk
209i	1.382	69.97	0.61	0.12	-1.79	-1.1	0.59	Low risk
209j	1.603	69.97	0.24	0.89	-2.05	-0.7	0.61	Low risk

TABLE- 47

COMPUTED LOGP AND DRUG LIKELINESS PROPERTY

Compound	Chem draw		Molinspi-ration	OSIRIS				
	ClogP	tPSA	milogP	ClogP	Solubility	Drug likeliness	Drug score	Mutagen-city
223a	1.92	83.41	0.259	-0.26	-1.87	4.53	0.95	Low risk
223b	2.27	83.41	0.66	0.13	-2.0	4.28	0.94	Low risk
223c	2.1	83.41	0.66	0.13	-2.0	4.35	0.94	Low risk
223d	2.1	83.41	0.982	0.13	-2.0	4.87	0.94	Low risk
223e	1.55	83.41	0.417	0.52	-2.13	4.88	0.93	Low risk

TABLE- 48

COMPUTED LOGP AND DRUGLIKELINESS PROPERTY 220a-f

Compound	**Chem. draw**		**Molinspi-ration**	**OSIRIS**				
	ClogP	**tPSA**	**milogP**	**ClogP**	**Solubility**	**Drug likeliness**	**Drug score**	**Mutagen-city**
221a	1.55	61.77	1.479	0.84	-2.34	1.88	0.87	Low risk
221b	2.04	61.77	1.928	1.15	-2.68	2.13	0.52	High risk
221c	2.11	61.77	2.157	1.45	-3.07	4.31	0.87	Low risk
221d	1.43	71	1.536	0.73	-2.35	2.27	0.42	High risk
221e	1.3	80.23	1.521	0.63	-2.37	4.25	0.89	Low risk
221f	1.62	61.77	1.18	0.63	-2.15	3.33	0.91	Low risk
o-toludine amide of 209a	2.04	61.77	2.28	1.15	-2.68	3.65	0.92	Low risk
o-anisidine amide of 209a	1.43	71	1.888	0.73	-2.35	3.65	0.92	Low risk

4.7.2. Anti bacterial activity

Literature survey showed pyrido[1,2-a]pyrimidines exhibit significant pharmacological properties. The synthesized compounds 2-oxo-2H-pyrido[1,2-a] pyrimidin-3(4H)-ylidene acetic acids(a-e) and their thiadiazole derivatives were subjected to antibacterial activity studies against *Escherichia-Coli* and *Staphylococcus aureus* by disc diffusion method against standard drug ciproflaxin. The tested compounds showed moderate activity against both the species as seen from the **Table-49**

TABLE - 49

ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

	Zone of inhibition(mm)			**Zone of inhibition(mm)**	
Compound	***Escherichia coli***	***Staphylococcus aureus***	**Compound**	***Escherichia coli***	***Staphylococcus aureus***
209a	10	10	222a	11	12
209b	10	10	222b	11	12
209c	10	11	222c	11	13
2209d	11	11	222d	12	13
209e	11	11	222e	12	13
Ciproflaxin	27	27	Ciproflaxin	27	27

4.7.3 Anti Cancer activity

The compounds **221a** and **221c** were tested for their cyto toxic effect on the human cervical cancer cell line (**HeLa**) Both the compounds showed cytotoxic effect on the cancer cells with LD $_{50}$ = 27.9µM for **221a** and 41 µM for **221c.** The results are graphically depicted in **Figure – 42 and 43.**

FIGURE- 50

ANTI CANCER ACTIVITY OF 221a

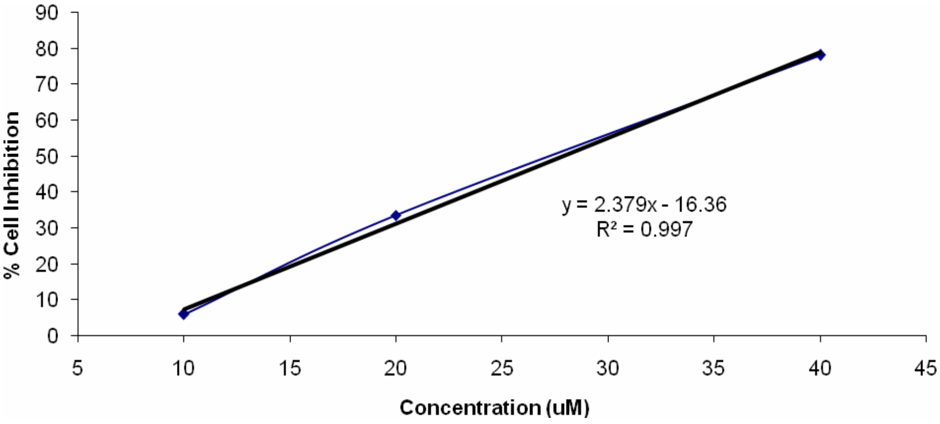
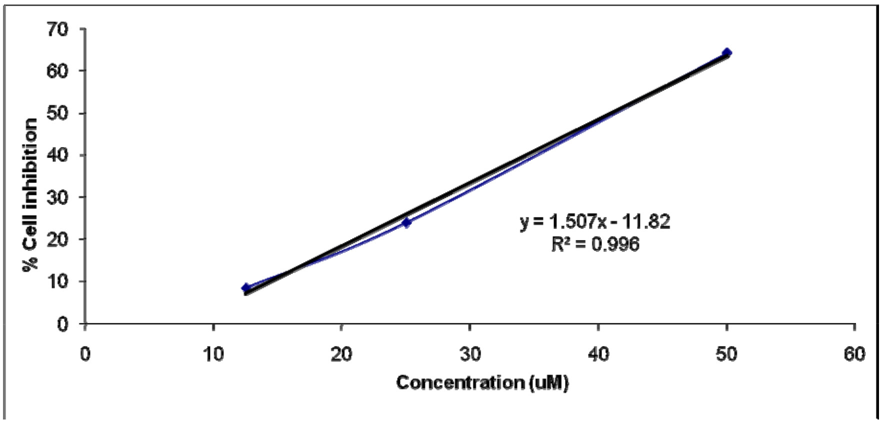


FIGURE -51

ANTI CANCER ACTIVITY OF 221c



The results of antibacterial and anticancer activity studies are photographed in plates 1 and 2.

PLATE - 1

ANTIBACTERIAL ACTIVITY OF THE COMPOUND 209b and 209c AGAINST *ESCHERICHIA COLI*

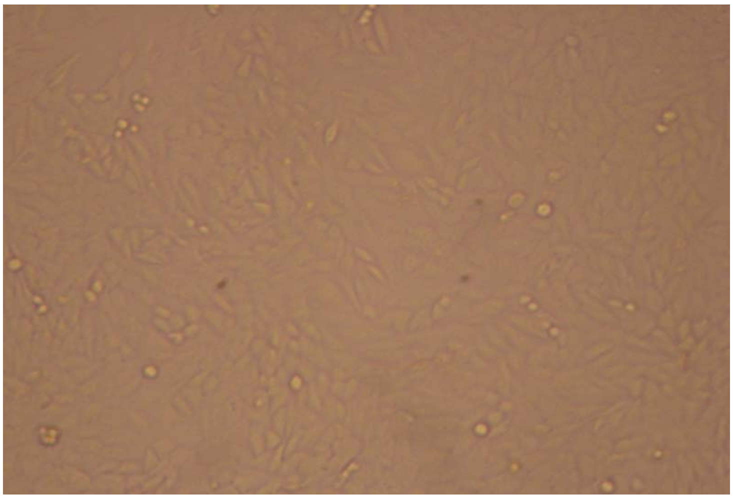
PLATE - 2

ANTIBACTERIAL ACTIVITY OF THE COMPOUND 209b and 209c AGAINST *STAPHYLOCCUS AUREUS*

PLATE -3

ANTICANCER ACTIVITY OF THE COMPOUND 220a AGAINST HUMAN CERVICAL CANCER CELL LINES

CONTROL



COMPOUND 220a

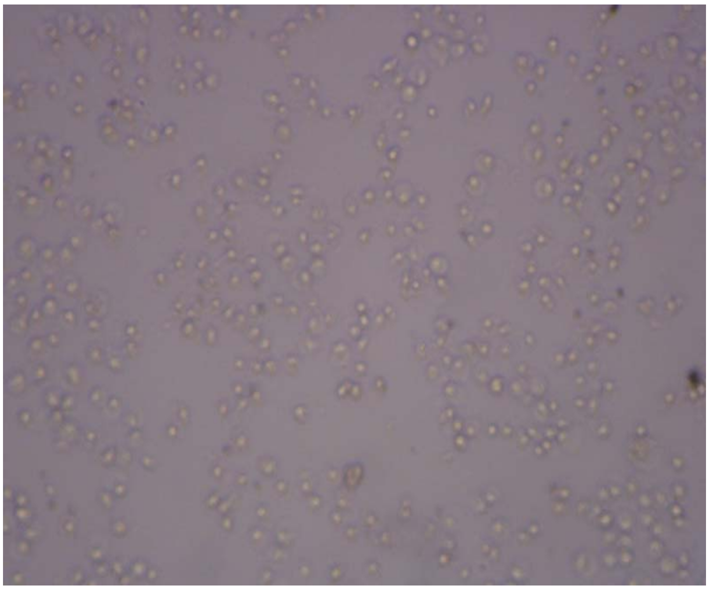
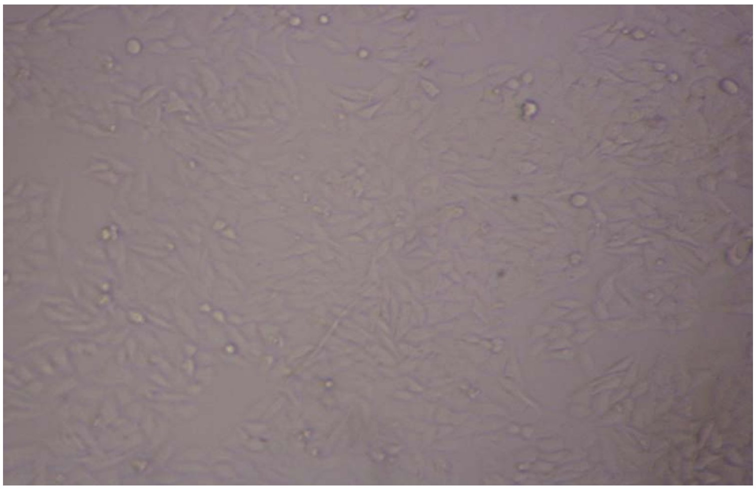


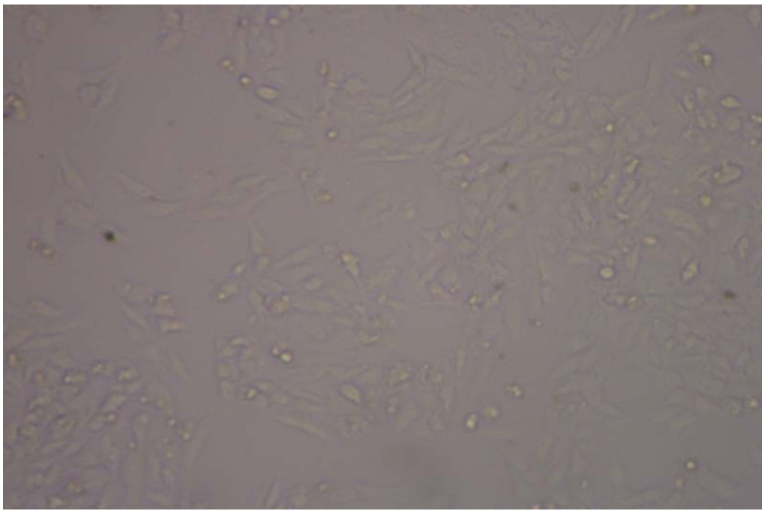
PLATE -4

ANTICANCER ACTIVITY OF THE COMPOUND 220a AGAINST HUMAN CERVICAL CANCER CELL LINES

CONTROL



COMPOUND 220c



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REFERENCE

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