^{13}C NMR and Mass spectral studies of Pyrido derivatives

By

Sridevi. C

13PCH015

A dissertation submitted to

Avinashilingam Institute for Home Science and Higher Education for Women, University

(estd. U/s 3 of ugc act 1956)

Coimbatore-641 043

In Partial Fulfilment of the Requirements for the Degree of Master of Science in Chemistry

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Certified as Bonafide Research Work

Signature of the Guide

Signature of the Head of Department

ACKNOWLEDGEMENT

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Every work on the back drop has the blessings of the **lord almighty**. Therefore submitting my reverential gratitude on the feet of the lord almighty, I deem it necessarily to thank all who rendered their help during the course of this study.

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SRIDEVI. C

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LIST OF ABBREVIVATION

NMR	- Nuclear Magnetic Resonance
IR	- Infrared
EtOH	- Ethanol
^{1}H-NMR	- Proton Nuclear Magnetic Resonance
^{13}C- NMR	- Carbon-13 Nuclear Magnetic Resonance
CNS	- Central Nervous System
MeOH	- Methanol
NIR	- Near Infrared
HPLC	- High Performance Liquid Chromatography
DME	- Dimethyl Ether
EMME	- Ethoxy Metylene Malonic Di Ethyl Ester
DPE	- 1,2-di(4-pyridyl)ethane
HCl	- Hydrochloric acid
ECF	- Eosinophil-Chemotactic-Factor
TEA	- Triethylamine
DMF	- Di Methyl Fluorine
NaN_3	- Sodium Nitrite
H_2O	- Water
EDC	- 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
HOBT	- Hydroxybenzotriazole
DIE	- N, N-Diazopropylethylamine
MDC	- Macrophage Derived Chemokine
DMSO	- Dimethyl Sulfoxide
$HClO_4$	- Perchloric acid
HIV	- Human immunodeficiency virus

TLC	- Thin Layer Chromatography
PPM	- Parts per million
KBr	- Potassium Bromide
HOMO	- Highest Occupied Molecular Orbital
LUMO	- Lowest Unoccupied Molecular Orbital
PTSA	- Para Toluene Sulphonic Acid
DCM	- Dichloromethane

INTRODUCTION

1. INTRODUCTION

Structure determination is a greater task for the synthetic and the natural products chemist, for the development of new materials, and the forensic chemist isolating drugs or toxins from a suspect or victim, and the environmental chemist examining the effects of materials contaminating soil, bodies of water, or the atmosphere, and the archaeological chemist tracing dietary information from food residues in pottery, and the biological chemist examining enzymatic mechanisms in the body. The quest for structural information on soils, liquids, or gases, on crystalline, powered, or glassy materials, on mixtures or pure compounds is a continuing challenge to chemists of every type.

Various forms of spectroscopy can provide a wide array of structural information in the most rapid fashion possible, for all phases of matter, and on mixtures as well as on pure compounds. The most common and useful forms of organic structural spectroscopy include IR, NMR and Mass spectroscopy techniques.

1.1 IR SPECTROSCOPY

Infrared radiation was discovered by astronomer **Sir William Herschel** in 1800. Infrared energy is emitted or absorbed by molecules when they change their rotational-vibrational movements. Infrared energy elicits vibrational modes in a molecule through a change in the dipole moment, making it a useful frequency range for study of these energy states for molecules of the proper symmetry. Infrared spectroscopy examines absorption and transmission of photons in the infrared energy range.

1.2 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

NMR spectroscopy is one of the best tools for the structural elucidation of organic compounds. It gives detail about the type, number and connectivity of particular atoms. NMR spectroscopy is used to identify the structure of both pure compounds and mixtures.

NMR always has been multidimensional methods. One dimensional (1D) NMR spectroscopy includes regular ^{1}H and ^{13}C carbon spectra of other methods, 3D and 4D experiments can also be done sometimes by running the pulse sequence from two or three 2D experiments in series.

1.3 CARBON-13 (NUCLEAR MAGNETIC RESONANCE)

^{13}C-NMR sometimes simply referred to as Carbon-13 NMR or Carbon NMR. ^{13}C NMR is an important tool in chemical structure elucidation in organic chemistry. It is analogous to proton NMR (^{1}H- NMR) and allows the identification of carbon atoms in an organic molecule just as proton NMR identifies hydrogen atoms, ^{13}C-NMR detects only the ^{13}C isotope of carbon because the main carbon isotope ^{12}C is not detectable by NMR since it has zero net spin.

^{13}C- NMR has a number of complications that are not encountered in proton NMR. The 1D ^{13}Carbon NMR experiment is much less sensitive than Proton (^{1}H) but has a much larger chemical shift range. In further contrast to ^{1}H- NMR, the intensities of the signals are not normally proportional to the number of equivalent ^{13}C atoms and are instead strongly dependent on the number of surrounding.

^{13}C- NMR is low natural abundance (1.108%) and proton decoupling means that spin-spin couplings are seldom observed. This greatly simplifies the spectrum and makes it less crowded. It's a low sensitivity nucleus that yields sharp signals and has a wide chemical shift range. A typical analysis of a ^{13}C- NMR spectrum consists of matching expected chemical shifts to the expected moieties. The general implications of these points are that ^{13}C-NMR spectra take longer to acquire than H-NMR, though they tend to look simpler.

1.4 MASS SPECTROMETRY

Mass spectrometry (MS) is a spectroscopic method for elucidating molecular structure and is one of the truly interdisciplinary methods in science. It originated in physics, has been applied throughout the biological and earth sciences and across the field of chemistry, and is of particular importance in environmental science. Mass spectroscopy is both a tool for accomplishing measurements in many areas of science.

Mass spectroscopy is distinguished by its extremely high sensitivity and by its applicability to samples in all physical states (including aqueous solutions and solid materials) and to samples of high as well as low molecular weight.

Mass spectroscopy is usually performed to determine the molecular weight of a compound(s). To accomplish this, one of the several ionization methods for producing intact molecular ions must be used. These methods generate either positive or negative ions related to the original molecule by adding or subtracting an electron, or by adding or subtracting an anion or cation.

1.4.1 USES OF MASS SPECTROSCOPY

- Molecular weight determination of pure compounds, mixtures
- Molecular formula determination of usually pure compounds.
- Molecular structure determination of pure compounds or mixtures by LC-MS, GC-MS, and MS-MS.
- Sequences determination of proteins, other biopolymers.
- Isotopic incorporation and fractionation of naturally and artificially labeled compounds (^{13}C, ^{2}H, ^{18}O, etc).

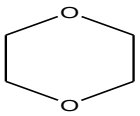
1.5 HETEROCYCLIC COMPOUNDS

There are various Organic compounds with different structures which can be acyclic or cyclic. Carbocycles are the cyclic systems containing only carbon atoms whereas the cyclic system containing carbons and at least one other element are called heterocyclic. Here the prefix hetero refers to the non carbon atoms present in the ring system where the common hetero atoms are nitrogen, oxygen or sulphur.

The most common hetero cycles are those having five- or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene. A molecule of pyridine contains a ring of six atoms five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each contain five-membered rings, composed of four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively.

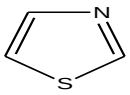
Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins and antibiotics are heterocyclic compounds.

Examples:



Dioxane

1

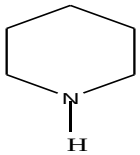


Thiazole

2

Ethylene oxide

3



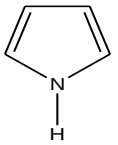
Piperidine

4

1.5.1 NITROGEN HETEROCYCLIC COMPOUNDS

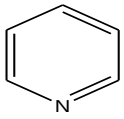
These are molecules containing nitrogen atoms along with carbon atoms in the rings like Pyridine and Pyrrole. Pyridine and Pyrrole rings consist of many biological materials which are obtained by strong heating. On strong heating of bones, an oily mixture of Pyridine and Pyrrole were formed in the 1850, but today they are prepared synthetically. Their chief commercial interest lies in their conversion to other substances, chiefly dyestuffs and drugs. Pyridine is used also as a solvent, a waterproofing agent, a rubber additive, an alcohol denaturant, and a dyeing adjunct.

Example:



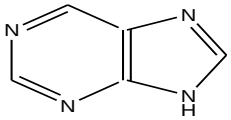
Pyrrole

5



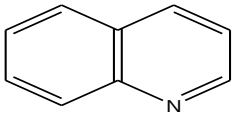
Pyridine

6



Purine

7



Quinoline

8

1.5.2 APPLICATIONS OF HETEROCYCLES

Heterocycles have an immense importance in biological aspect and in industries by their largest classical divisions. These compounds have their applications in medicine, agriculture, photodiodes and great advantage by the drug industry. The most widely used drugs can also be synthesised from vitamin thiamin containing a pyrimidine ring and synthetic barbiturates such as amobarbital (amylobarbitone).

Piperidines have valuable medicinal chemistry properties the alkaloids and Palinavir have been reported to be highly potent inhibitors in the treatment of the immuno deficiency virus (HIV). Substituted piperidine derivatives find applications as anticancer, antihistaminic, bactericidal, CNS stimulant and depressant, herbicidal, insecticidal, and fungicidal agents. **Li et al ., (2014)**.

Anastrozole is an aromatase-inhibiting drug approved for the treatment of breast cancer after surgery, as well as for metastasis in both pre and postmenopausal women. Thiazoles are of great biological importance. This ring system occurs in thiamin(thiamine, vitamin B_1), the bacitracin and penicillin antibiotics (from a bacterium and a mold, respectively), and in numerous synthetic drugs, dyes, and industrial chemicals. Synthetic drugs belonging to the thiazole family include the antimicrobial agents sulfathiazole and acinitrazole, the antidepressant pramipexole,

and the antiasthmatic drug cinalukast. These also has specific importance associated with many physiological activities

Heterocycles are chemically more flexible and are able to respond to the many demands of biochemical system. Many polycyclic compounds containing a phenoxazine ring are used as biological stains, fabric dyes, and light-emitting materials in dye lasers (e.g., cresyl violet and nile blue). The biological system such as vitamins, enzymes, coenzymes, nucleic acids, ATP and serotonin all are the heterocyclic compounds , it can be used as provision of the energy, transmission of nerve impulse, sight, metabolism and the transfer of hereditary information. Adenosine monophosphate, diphosphate, and triphosphate (AMP, ADP, and ATP, respectively) are important participants in energy processes in the living cell.

Many of the heterocycles are active in pharmaceuticals and biological aspect and are active in agrochemicals while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are also heterocyclic in nature.

Heterocyclic compounds may be classified as aliphatic and aromatic heterocycles. Natural heterocyclic compounds like papaverine, theobromine, quinine, emetine, theophylline, atropine, reserpine and morphine and synthetic heterocyclic compounds like diazepam, chlorpromazine, isonized, meteronidazole, azidothymidine, antipyrine, can and do participate in chemical reactions in the human body.

The constantly accelerating rate of research and development in heterocyclic chemistry suggested that enormous numbers of heterocyclic systems are well known and this number is increasing very rapidly. **(Dua et al ., 2011).**

i. OBJECTIVES

^{13}C signals NMR is the method of choice for structural investigations of complex molecules such as natural products, synthetic as well as biological oligomolecules and macromolecules. The structural elucidation of small molecules using mass spectrometry plays important role in analytical approaches. In this context,

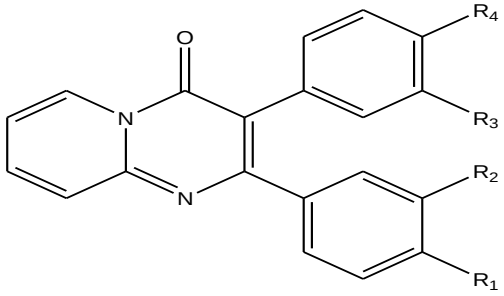
- The present study was carried out to study ^{13}C NMR of 5-(pyridine-2-ylamine)-5-oxopentanoic acid and 1-acetyl -1H-pyrido [1, 2-a] pyrimidin-4(9AH)-one.
- To predict ^{13}C shift values using Chem. draw ultra 10.00
- To compare the predicted and experimental ^{13}C NMR values.
- To study the mass spectral pattern of the compounds 5-(pyridine-2-ylamine)-5-oxopentanoic acid and 1-acetyl -1H-pyrido [1, 2-a] pyrimidin-4(9AH)-one.

REVIEW OF LITERATURE

EVIEW OF LITERATURE

- 2,3-diphenyl-4H-pyrido[1,2-a]pyrimidin-4-one **9** derivative was examined by **Del et al ., (2014)** as novel compounds for its effects in vitro on induced-cell proliferation and activation in human aortic smooth muscle cells (HAoSMCs) and in human umbilical vein endothelial cells (HUVECs). When compared with flavonoids, apigenin and quercetin, the novel compound was not toxic for HUVECs, even at high concentrations and for long incubation times.

In HUVECs, it inhibited the cytokine-induced vascular cell adhesion molecule-1 expression, but not the cyclooxygenase-2 (COX-2) expression. Instead, in HAoSMC, it inhibited the induction of COX-2 expression and the relative release of prostaglandin E2. In addition, it inhibited the transcription of the matrix metalloproteinase-9 and its activity. Its multiple and tissue-specific function, 2-(3,4-dimethoxyphenyl)-3-phenyl-4H-pyrido[1,2- a]pyrimidin-4-one might replace or assist the action of current drugs in order to promote a functional repair of damaged wall.



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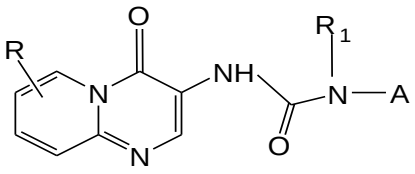
- Novel pyrido[1,2-a]pyrimidin-4-ones **10,11,.12,13** have been synthesized and evaluated by **Mane et al.,(2014)** for their antimalarial activity by SYBR Green I assay against erythrocytic stages of chloroquine (CQ) and also for the antiplasmodial activity of forty two pyrido [1,2-a]pyrimidin-4 one derivatives by SYBR Green Assay was carried out. Only two compounds viz. 3-fluorobenzyl (4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl) carbamate and 4-oxo-N-[4-(trifluoromethyl)benzyl]- 4H-pyrido[1,2-a]pyrimidine-3-carboxamide

showed moderate antimalarial activity in the whole series. Structural activity relationship (SAR) studies displayed the antimalarial activity was due to the unsubstitutedpyrido [1,2-a]pyrimidine. Based on the activity profile of the reported compounds it was concluded that pyrido [1,2-a]pyrimidin-4-one ring skeleton can be considered as a lead structure for further chemical optimization for obtaining potential antimalarial compounds.



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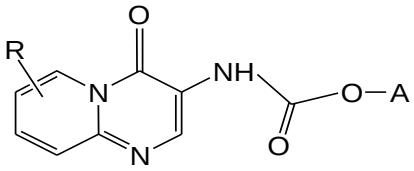

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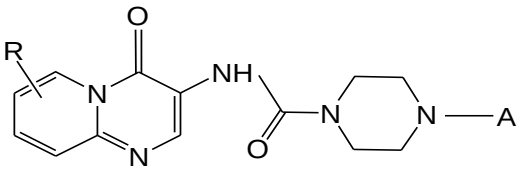

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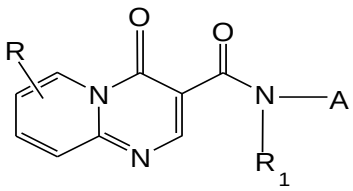

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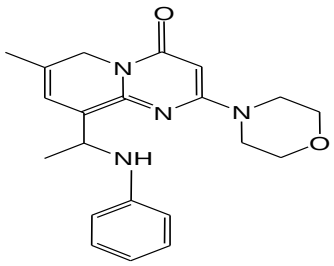
Where : R = H, 8-CH_3, 7-Cl, 4-C_6H_4OCH3
R1 = H, Alkyl
A = Allkyl / heteroaryl or alkyl

Pyrido [1,2-a]pyrimidine-4-one derivatives synthesized for potential antimalarial activity.

- The experiment based on the docking on TGX-221 in a PI3Kb homology model, was designed by **Barlaam et al., (2014)** for the synthesis of 9-(1-anilinoethyl)- 2-morpholino-4-oxo-pyrido[1,2-a]pyrimidine-7-carboxamides **14,15,16** as PI3Kb/d inhibitors. Structure–activity relationships and structure–property relationships around the aniline and the amide substituents were studied.



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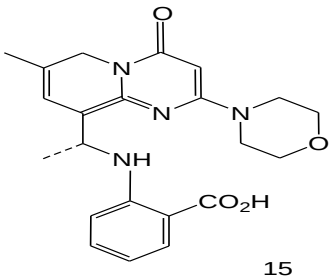

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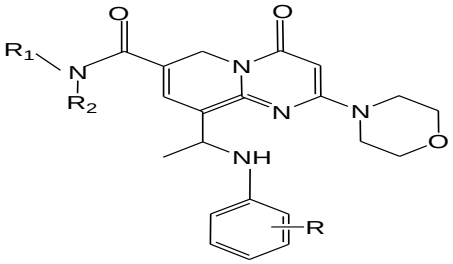

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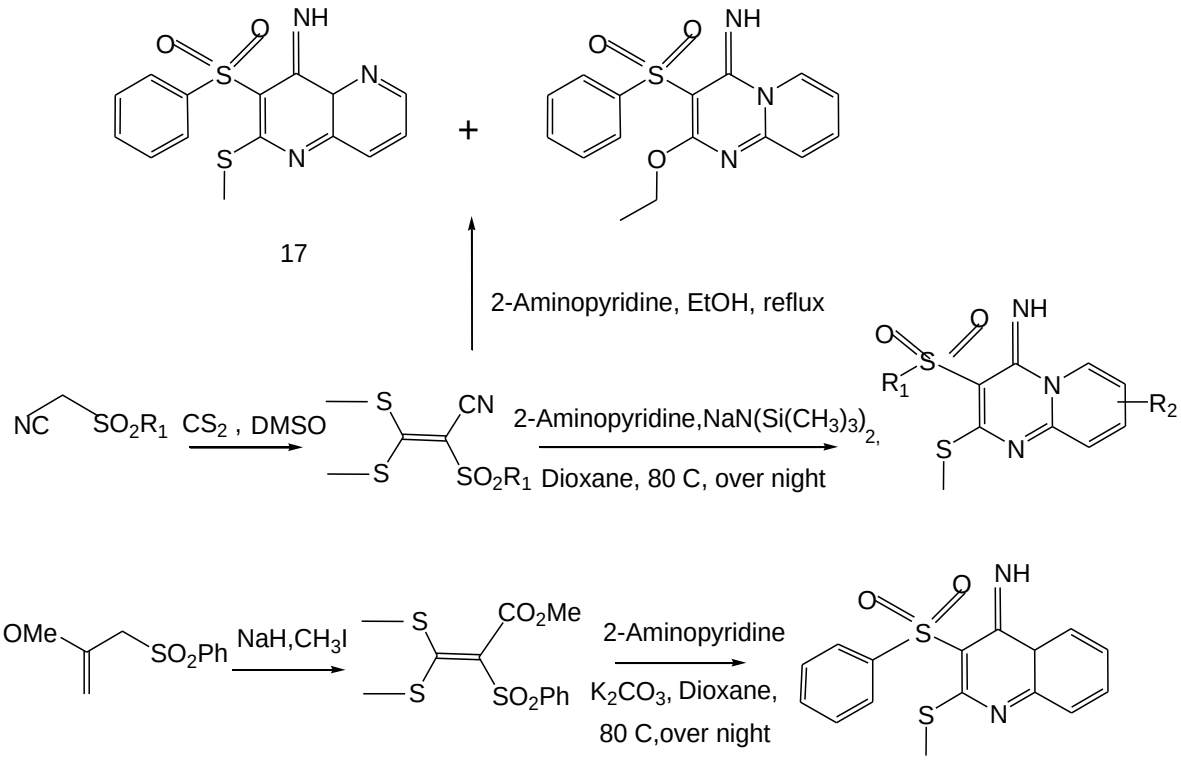
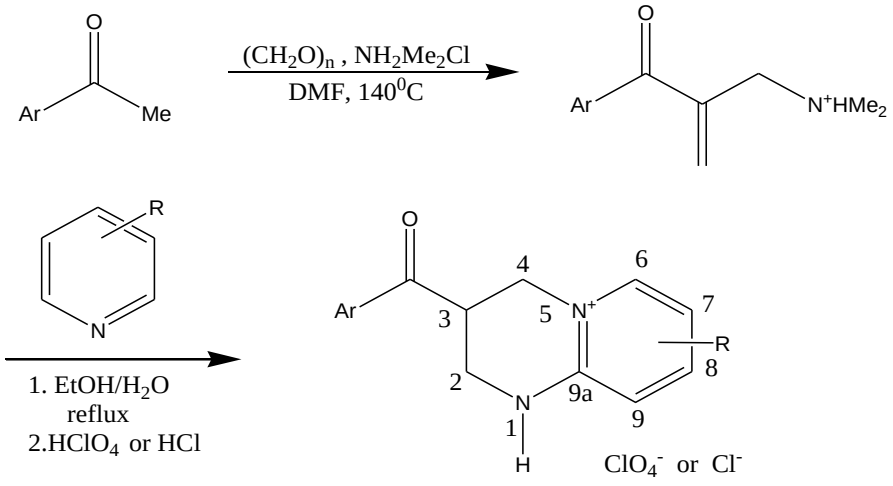
- **Shuanghua et al., (2014)** reported the synthesis of derivatives of 2-(methyl thio)-3-(phenyl sulfonyl)-4H-pyrido [1,2-a] pyrimidin-4-imine Structural solutions to the observed metabolic instability of **17** were identified using a human microsomal assay however, modifications that provided oxidative stability, compromised 5-HT6 potency. Molecular docking of key compounds in a homology model of the human 5-HT6 receptor was used to rationalize the structure–activity relationship (SAR) findings. In pharmacokinetic experiments, compound **17** displayed good brain uptake in rats following intra-peritoneal administration, but limited oral bioavailability.



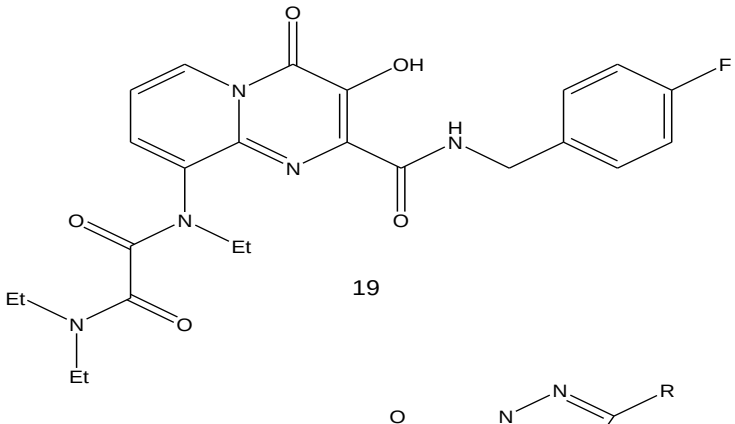
- 1,2,3,4-tetrahydro-pyrido[1,2-a]pyrimidinium perchlorates and chlorides **18**, with and without methyl substituent's in the unsaturated part of the heterocycle, were analysed by **Girreser et al ., (2013).**



18

Data set of $_1$^{1}H, ^{13}C, ^{15}N and ^{35}Cl chemical shifts in DMSO-d6. ^{1}H, ^{13}C and ^{1}H, ^{15}N long range couplings were investigated in structure elucidation. The influence of the methyl substituents was analyzed on the proton, carbon and nitrogen shifts. A significant effect of the counter ion on some chemical shifts of the nuclei was observed thus allowing the indirect detection of the anion.

- The study done by **Hajimahdi et al ., (2013)** indicated that 1,3,4-oxadiazole- and 1,3,4-thiadiazole-substituted 4-oxo-4H-pyrido[1,2-a]pyrimidines **19, 20** were suitable to design anti-HIV agents and the compounds were completely safe and exhibited no cytotoxicity. Most of the compounds displayed moderate HIV-1 inhibition rate. Where the most active compounds exhibited activity against HIV-1 virus (NL4-3) inhibition values of 51 and 48 %. This study revealed that the anti-HIV activity of the above mentioned compounds involved a metal chelating mechanism.



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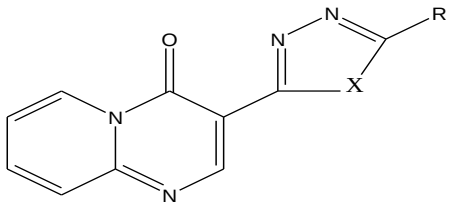
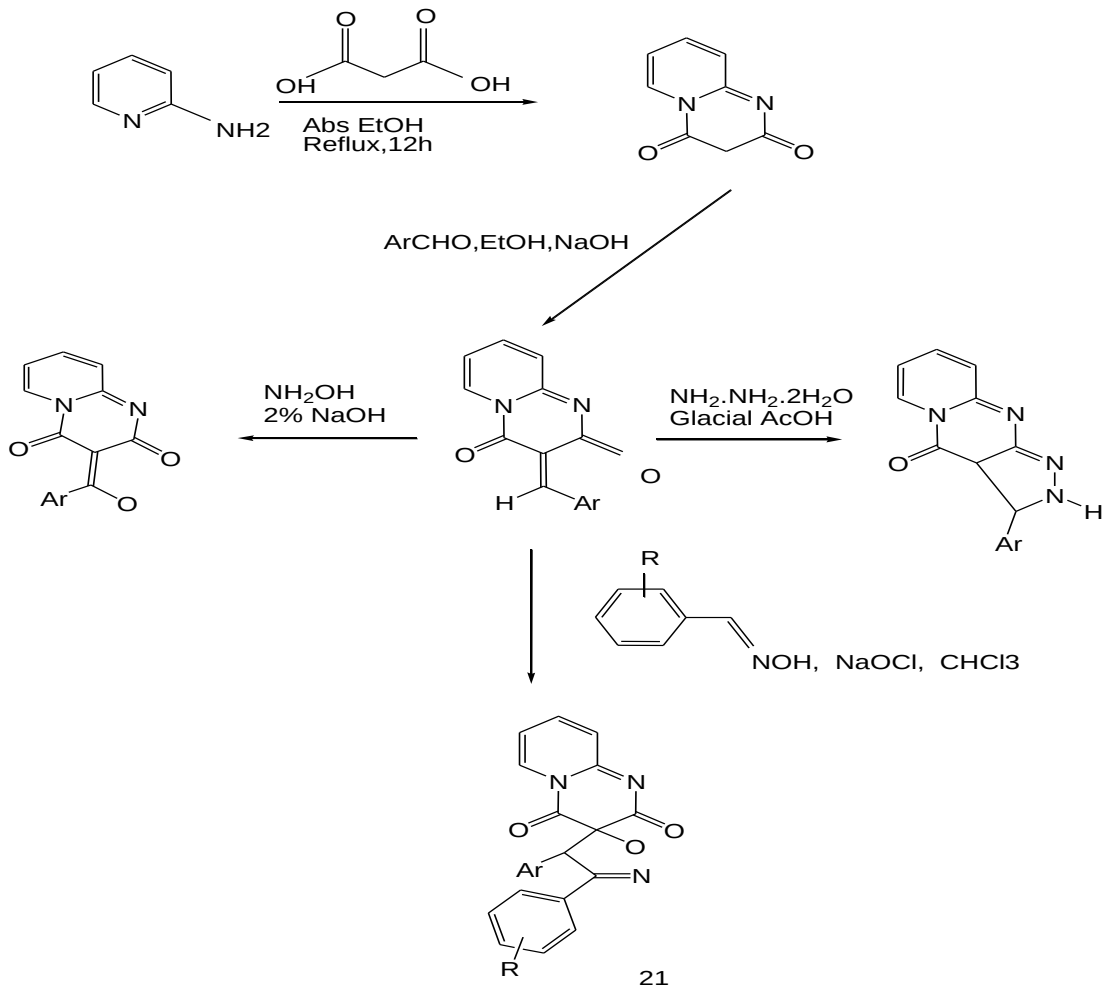


20

- **Bishnoi et al., (2013)**, developed a method for the synthesis of 4-(substituted phenyl)-3-(3-substitutedphenyl)4*H*spiro[isoxazole-5,3_-pyrid[1,2*a*]pyrimidine] 2_,4_-dione, 3-(4-substituted phenyl)- 3*H*- isoxazole [3,4-*d*] pyrido [1,2-*a*] pyrimidin-4-(3a*H*)-one and 3-(4-substituted phenyl) 3,3a-dihydropyrazolo[3,4-*d*]pyrido[1,2-*a*] pyrimidin-4-(2*H*)-one **21** which consists of the conversion of 2*H*-pyrido[1,2-*a*]pyrimidine- 2,4(3*H*)-dione to chalcones and their 1,3-dipolar

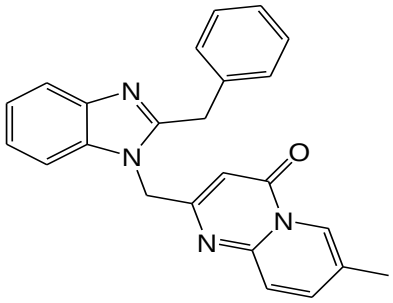
cycloaddition with appropriate aldoximes to yield spiro compounds and heterocyclization using amines to yield isoxazolines and pyrazolines. The series of heterocycles synthesized were evaluated for their antimicrobial and antitubercular activity. The results showed that among the spiro compounds, the one having benzo [*d*] [1,3] dioxole as a substituent as a potent inhibitor for both bacterial and fungal strains, however no active anti tubercular compound was identified.



Synthetic route for cyclization products of 3-(4-substituted benzylidene)-2H-pyrido [1,2-a] pyrimidine 2,4-(3H)-diones.

- **Guo et al., (2013)** describe the 2-((1H-benzo[d]imidazol-1-yl) methyl)-4H-pyrido[1,2-a]pyrimidin-4-ones **22-25** as potent and selective PKM2 activators which were found to have a novel binding mode. The compound was used as

molecular tools to probe the biological effects of PKM2 activation on cancer cells.



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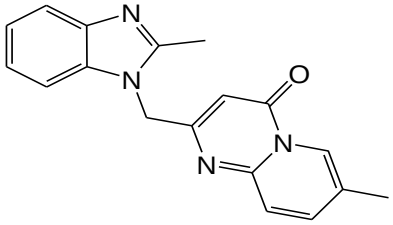

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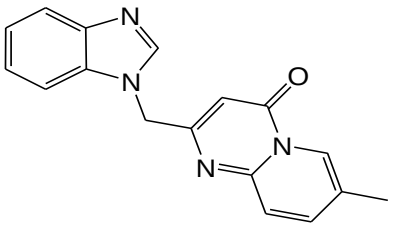

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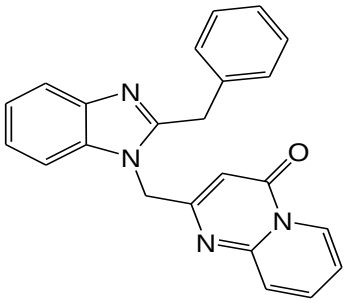
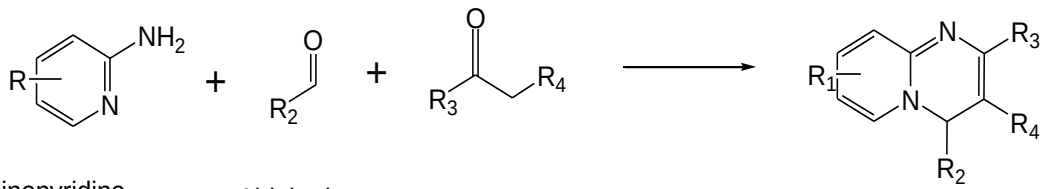


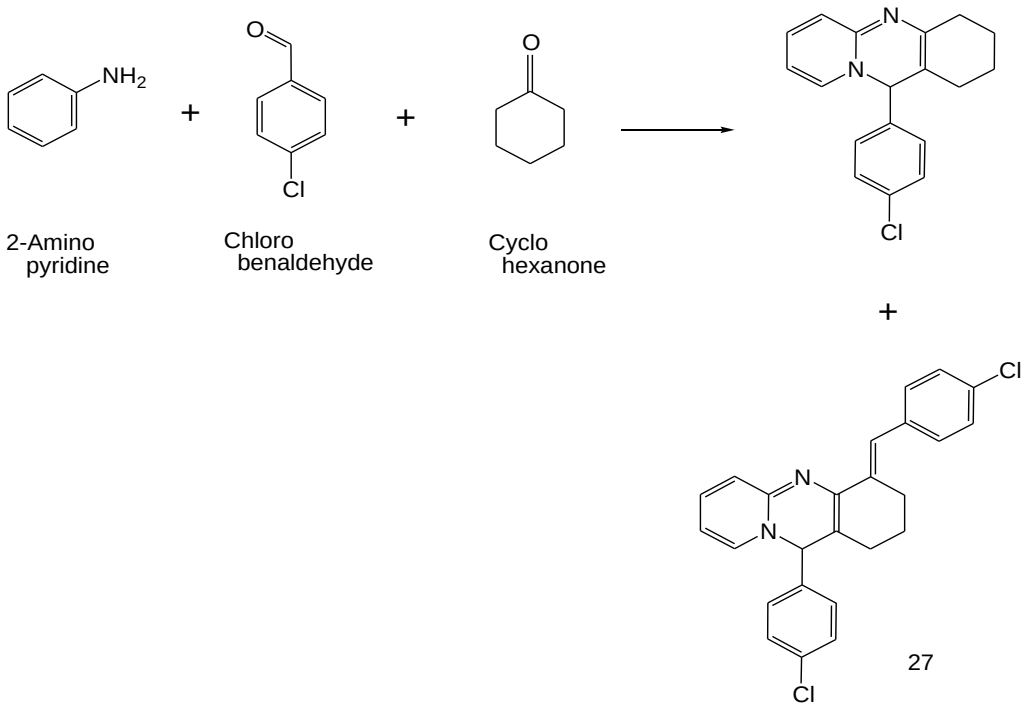
25

- A one – pot three - component reaction involving condensation of 2-aminopyridines, aldehydes, and ketones/aldehydes under trifluoro methane sulfonic acid catalysis was carried out by **Yang et al., (2013).** The multicompound reaction was simple, and was applied for the synthesis of highly substituted 4H-pyrido [1, 2-a] pyrimidines **26, 27**.

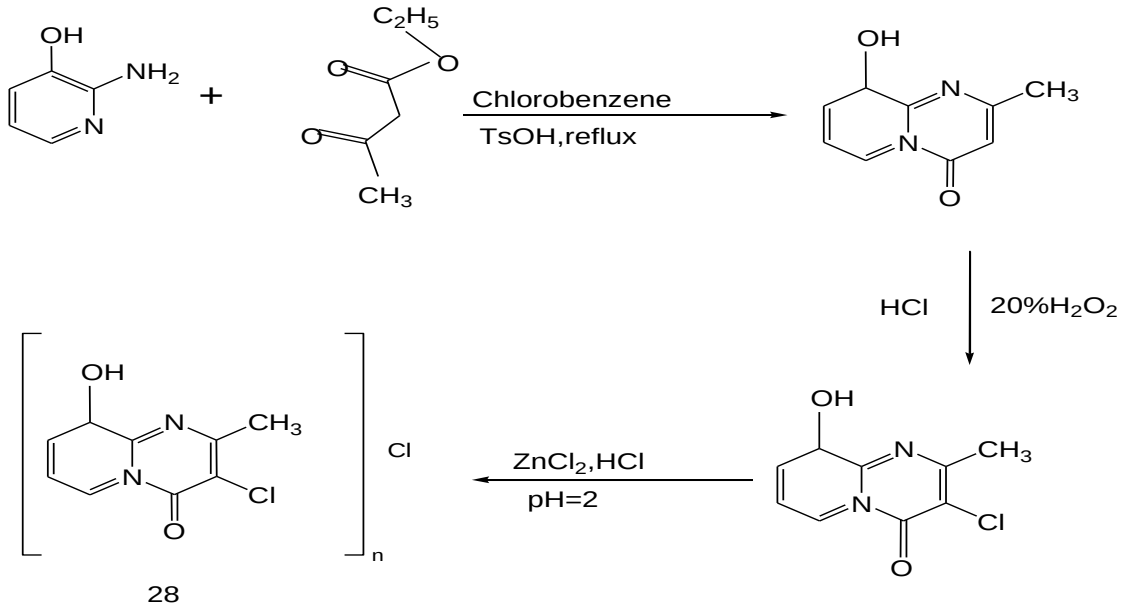


2-Aminopyridine Aldehydes Ketones / Aldehydes

26

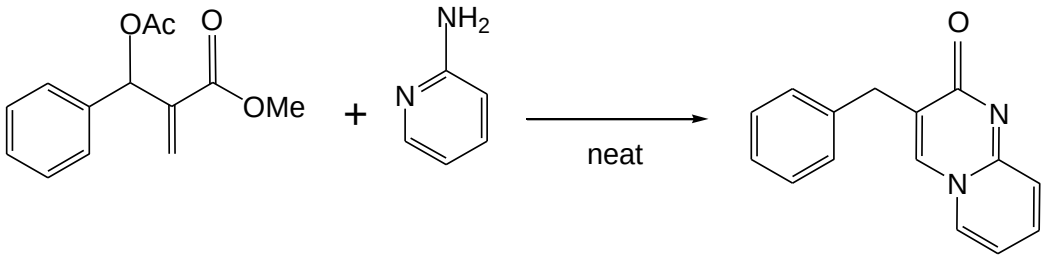


- A distinct compound, 2methyl-3chloro-9-hydroxy-4H-pyrido[1,2a]pyrimidine-4-one (MCHPP), has been prepared and characterized by **Zhang et al., (2013).** A study on the interaction of the title compound **28,** with ct DNA was also carried out. The results from the fluorescence and viscosity studies suggested that the compound interacts with ct DNA through a groove mode of binding. The synthesized compound was characterized by ^{1}H NMR and X-ray crystallography.



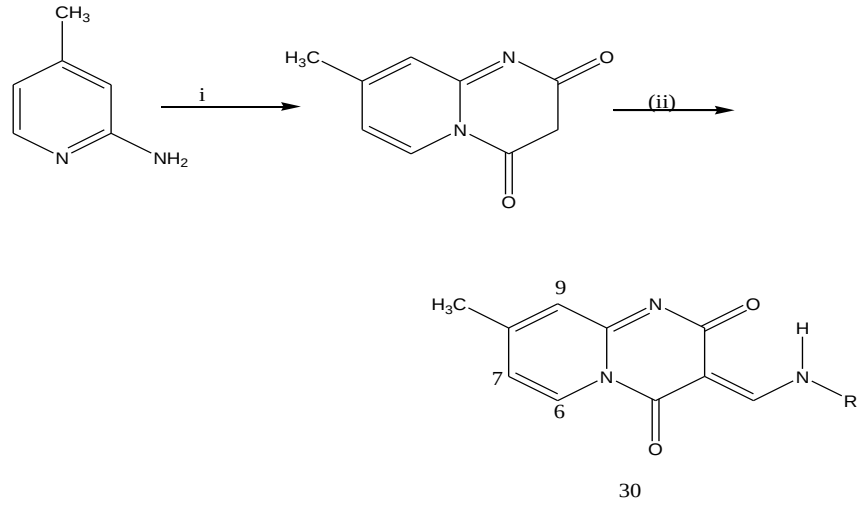
28

- A rapid synthesis of 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-one **29** derivatives by means of cyclocondensation of 2-(acetoxy(aryl)methyl)acrylates with 2-aminopyridines using microwave irradiation under neat condition was reported by **Satyanarayana et al.,(2013).** The major advantages of this reaction were,
    - reaction times
    - high conversions
    - catalyst and solvent-free conditions
    - Operational simplicity.



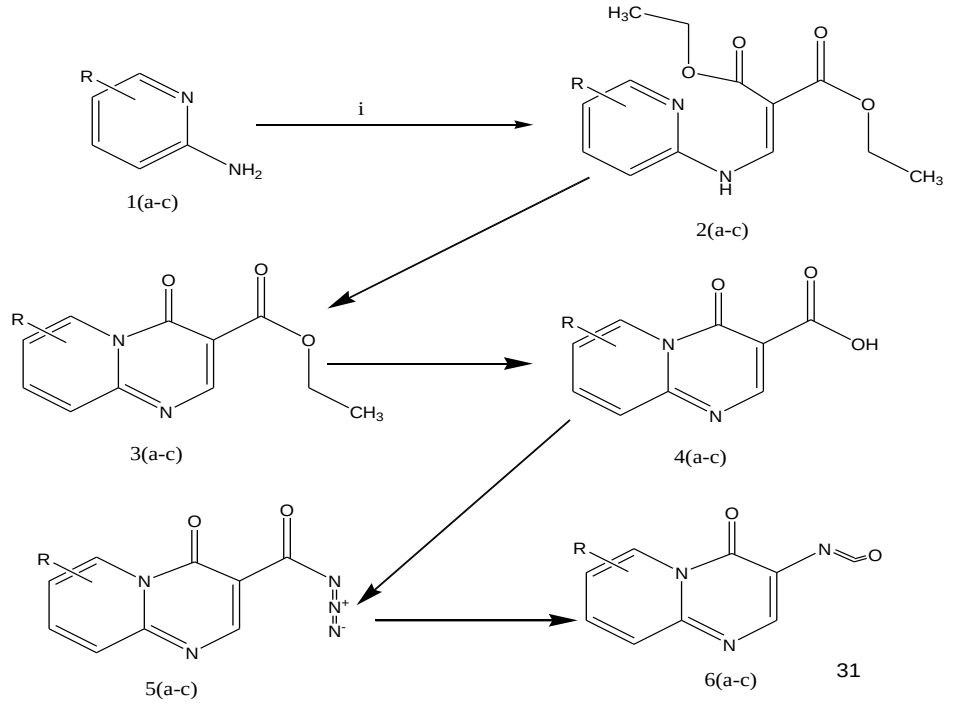
Reaction of Baylis - Hilman acetate with 2-aminopyridine 29

- 5-substituted-8-methyl-2H-pyrido [1,2-a]pyrimidine-2,4(3H)-diones **30** were reported by **Rauf et al ., (2012).** The chemical structures of all the compounds were elucidated by IR, ' H-NMR, ^{13}C-NMR and elemental analysis data. The synthesized compounds were screened for urease inhibition activity, by the phenol hypochlorite method. This study suggestsed that the compounds bearing sulfanylanilino and 4-nitrobenzohydrazide moieties possess significant urease inhibition activity. These compounds may have more tendencies to chelate with the nickel ions required for the activity of the enzyme. The same two compounds also exhibited anti-urease activity comparable to thiourea and also were potent inhibitors of the urease enzyme even at lower concentrations.



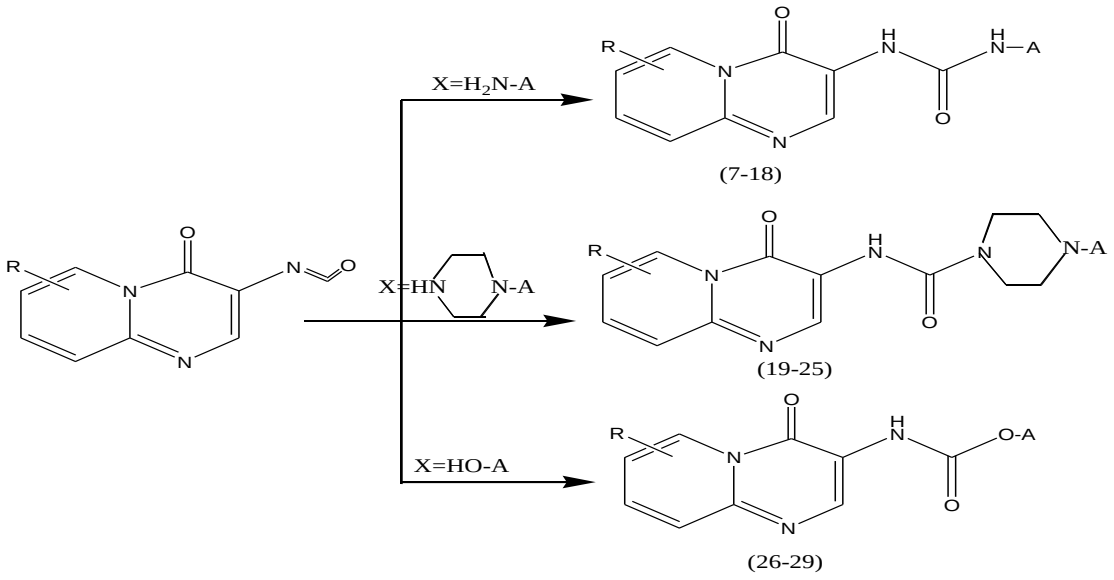
30

- Thirty two pyrido[1,2-a]pyrimidin-4-one derivatives **31&32,** were synthesized and was assessed for parasitic-enzyme-specific inhibitors and FP-2 inhibitors. The compounds showed good FP-2 inhibitory potential. Hence these compounds can serve as lead compounds for further development of potent FP-2 inhibitors and hence potential antimalarial drugs. **Mane et al ., (2012).**



31

Reagents and conditions: (i) EMME, reflux (ii) DPE, reflux (iii) HCl,reflux (iv) (a)ECF, TEA, DMF,0^0C(b). NaN_3, H_2O, 0^0C(v) toluene, reflux.

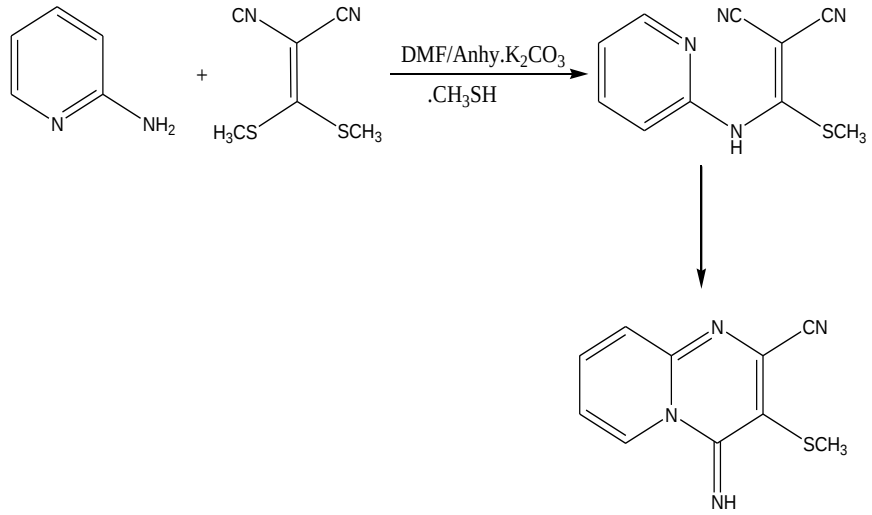


Reagents and conditions: (i) X, toluene, reflux.

32

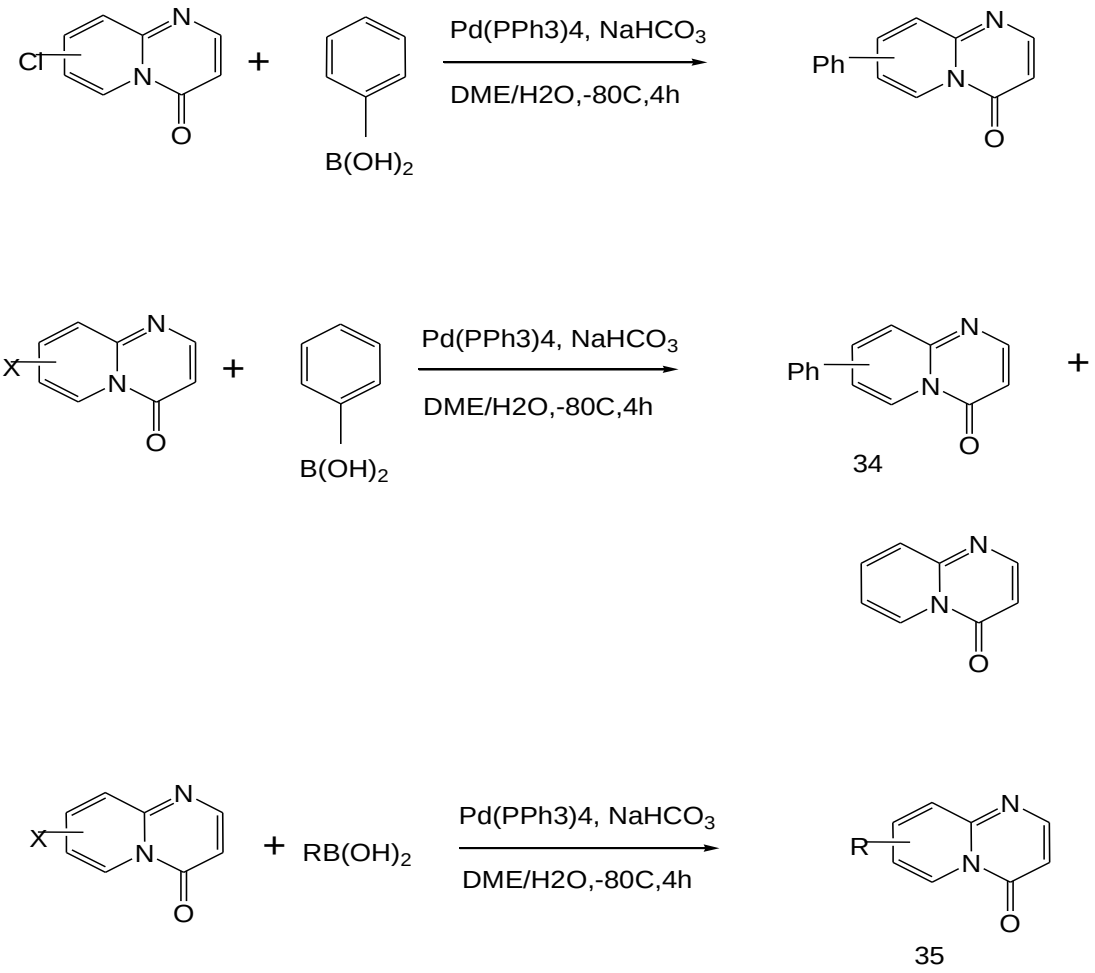
Reagents and conditions: (i)X, EDC,HOBT, DIEA, MDC, 0^0C,RT.

- The synthesis of 3-cyano-4-imino-2-methylthio-4H-pyrido[1,2-a] pyrimidine derivatives **33** were reported by **Vartale et al ., (2012)** by the reaction of bis (methylthio) methylene malononitrile and 2-amino pyridine in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate. The compounds have been screened as potent antioxidant agents. The results showed that the compound having a p-chloro aniline group on the imino pyrido[1,2-a]pyrimidine moiety as better antioxidant agent.

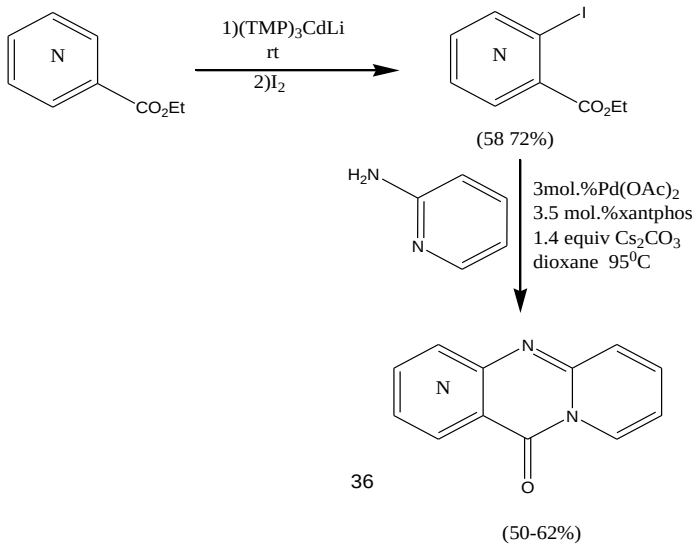


formation of fused pyrido(1,2-a)pyrimidine. 33

- The palladium-catalyzed Suzuki–Miyaura cross-coupling reactions were carried by **Moln´ar et al., (2011)** for the synthesis of aryl **34, 35** vinyl derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in excellent yields. The reaction sequence for the halogen atoms at different positions of this bicycle was 8 ≥ 2 > 9 > 7> 3, which was predicted almost correctly by the rule of Handy and Zhang. In accordance with the sequence of reactivity I > Br > Cl was observed at each position. 6-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was also prepared by thermal cyclization of isopropylidene (6-phenylpyrid-2-ylamino) methylenemalonate, together with a small amount of 7-phenyl-1,4-dihydro-1,8-naphthyridin-4-one.



- Pyridine nitriles and esters were directly metalated using $(TMP)_3CdLi$ in tetrahydrofuran at room temperature by **Ababsa et al ., (2010).** The 2-, 3-, and 4-cyanopyridines were treated with base for two hours, trapped with iodine to form iodo derivatives **36** with the yield of 32 to 61%. Similarly pyridine esters were synthesized to ethyl-3-iodopicolinates and isonicotinate. Ethyl -4-iodonicotinate was also formed under the same condition.

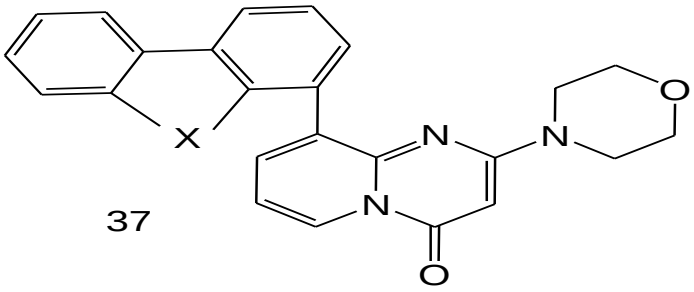


(50-62%)

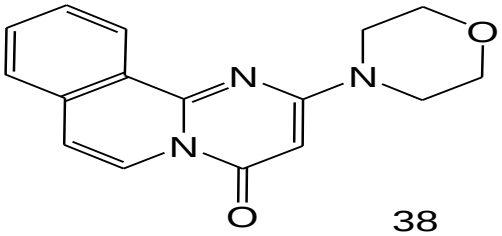
The ethyl iodopyridinecarboxylates obtained were involved in a one-pot palladium-catalyzed cross-coupling reaction / cyclization using 2-aminopyridine to afford new polycyclic compounds containing a pyridopyrimidinone moiety and were evaluated for bactericidal activity against *Pseudomonas aeroginosa*, Fungicidal activity against Fusarium, Candida albicans and anticancer activity on liver carcinoma cell line (HEPG2) , human breast carcinoma cell line (MCF7).

- **Cano et al., (2010)** investigated the possibility of replacing the chromen-4-one scaffold of previously identified DNA-PK inhibitors, with isosteric pyridopyrimidin-4-one **37** and **38** quinolin- 4 one heterocycles, and have elucidated the effects of introducing prospective water-solubilizing groups on the pendent dibenzothiophen-4-yl and dibenzofuran-4-yl substituents. The inhibitors were synthesized by employing a multiple-parallel approach in which the two heterocyclic components were assembled by Suzuki-Miyaura cross-coupling. Potent DNA-PK inhibitory activity was generally observed across the compound series, with structure-activity studies indicating that optimal potency resided in pyridopyrimidin-4-ones bearing a substituted dibenzothiophen-4-yl group. Several of the newly synthesized compounds (e.g., 2-morpholin-4-yl-N-[4-(2-morpholin-4-yl-4-oxo-4H-pyrido[1,2-a]-pyrimidin-9-yl)dibenzothiophen-1-yl] acetamide) combined high potency against the target enzyme with

promising activity as potentiators of ionizing radiation-induced cytotoxicity in vitro.

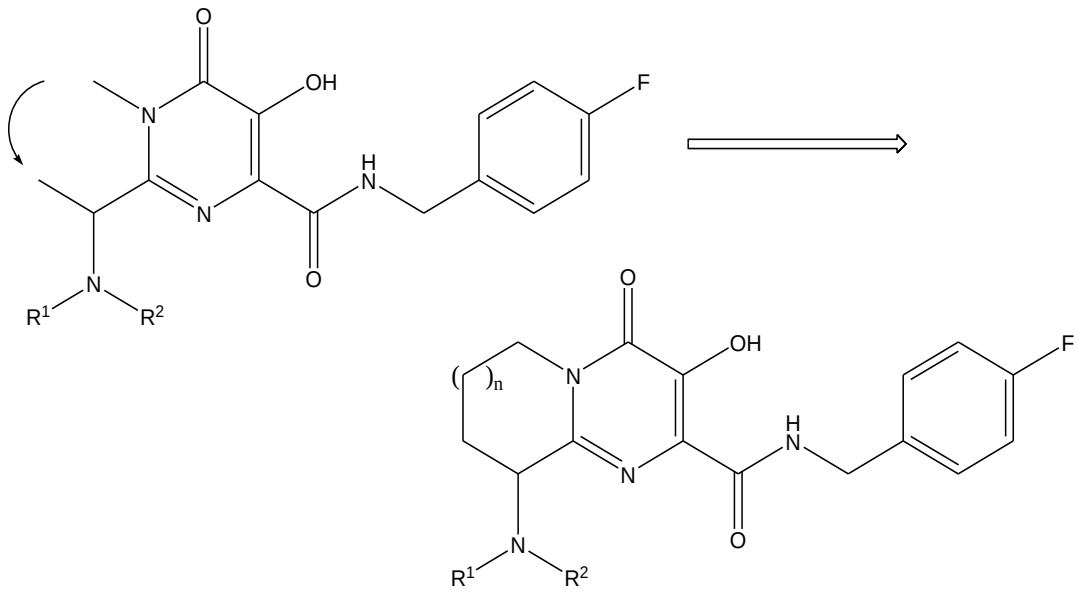


37



38

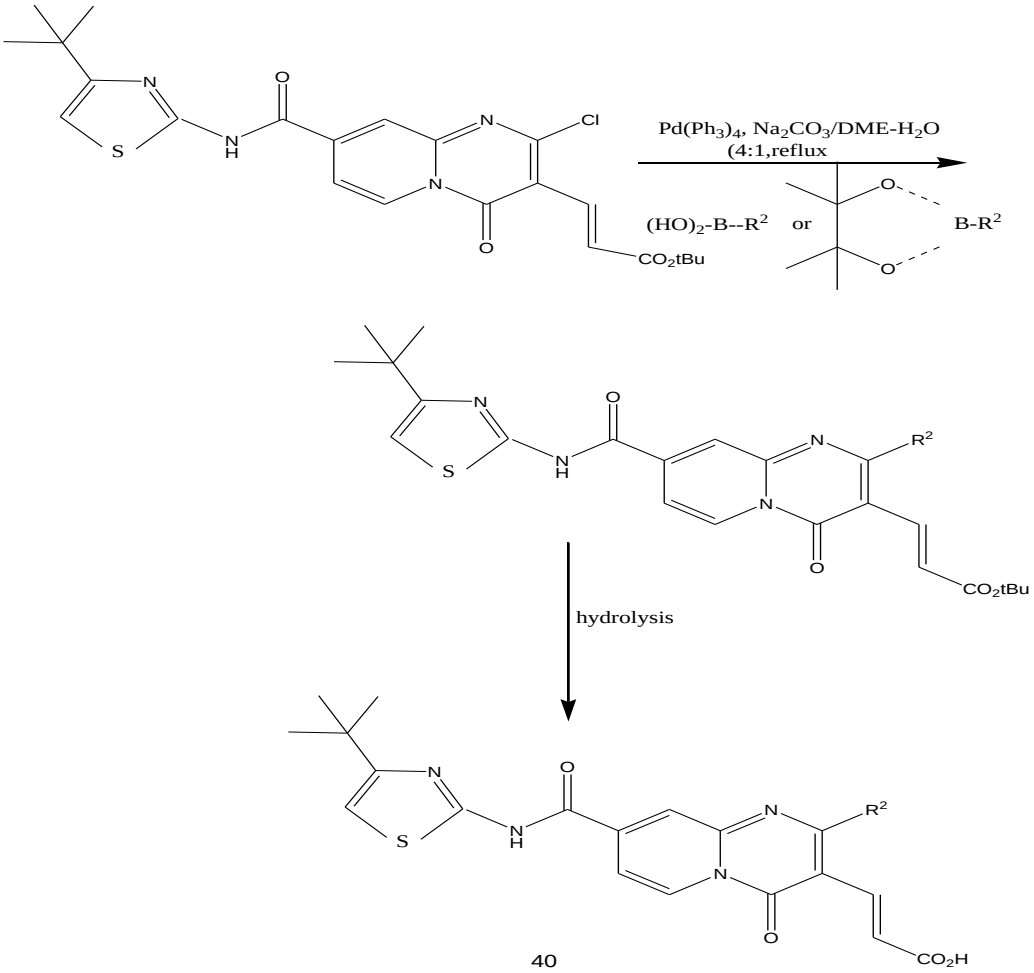
- Amine, amide, sulfonamide, sulfamide, and ketoamide derivatives of bicyclic pyrimidinones **39** were evaluated for HIV integrates inhibitors. Introducing a suitable substituted amino moiety modulated the physical-chemical properties of the molecules and conferred nanomolar activity in the inhibition of spread of HIV-1 infection in cell culture, leading to the ketoamide, which proved to be a very potent and selective HIV integrase inhibitor and orally biovailable and with good pharmacological profile in preclinical species. **Muraglia et al ., (2008).**



6a: n=0
6b: n=1
6c: n=2

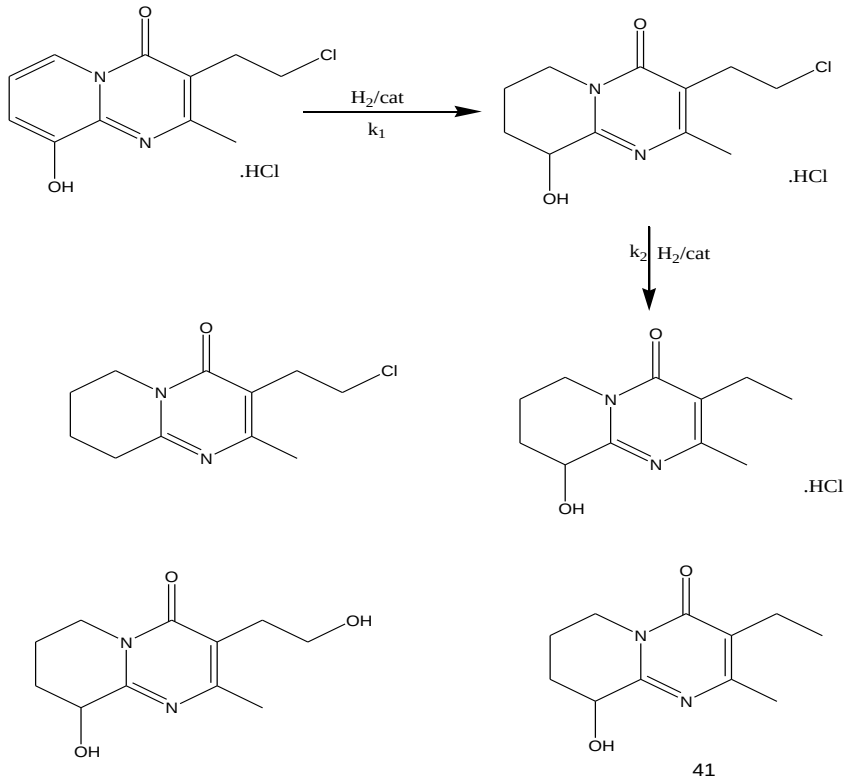
39

- **Yoshida et al., (2006)** synthesized a series of 4-oxo-4H-pyrido[1,2-a] pyrimidine derivatives **40**, by the Suzuki cross-coupling method and evaluated their ability to potentiate the activity of the fluoroquinolone levofloxacin (LVFX) and the anti-pseudomonas β-lactam aztreonam (AZT) in *Pseudomonas aeruginosa*. Benzyl amine analogues that exhibited improved solubility stimulated the exploration of other substituent's on benzylic nitrogen atom and culminated in the morpholine analogue, which showed potentiation activity in vivo and a reasonable safety profile in an acute toxicity assay.



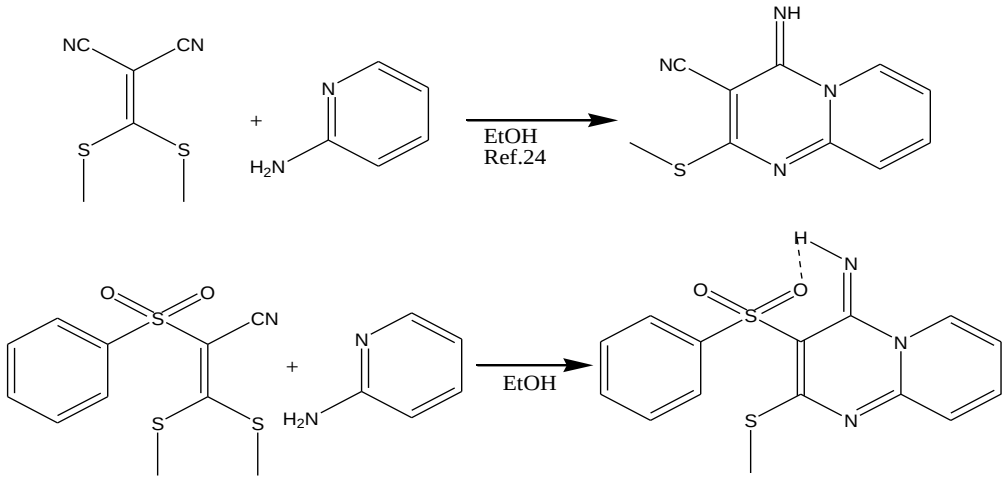
40

- Analytical technologies were used by **Smet et al ., (2005)** to solve the problem of selectivity in the hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one monohydrochloride to 3-(2–chloroethyl) -6,7,8,9– tetrahydro–9–hydroxyl–2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one monohydrochloride **41**. The results indicated that both mid-IR and near-IR (NIR) were suitable for in-line analysis of the hydrogenation but NIR was used in the production environment due to easier implementation. NIR model was developed by correlating the NIR results with HPLC results for a laboratory-scale hydrogenation reactor and production batch data was used to adjust and confirm this method.



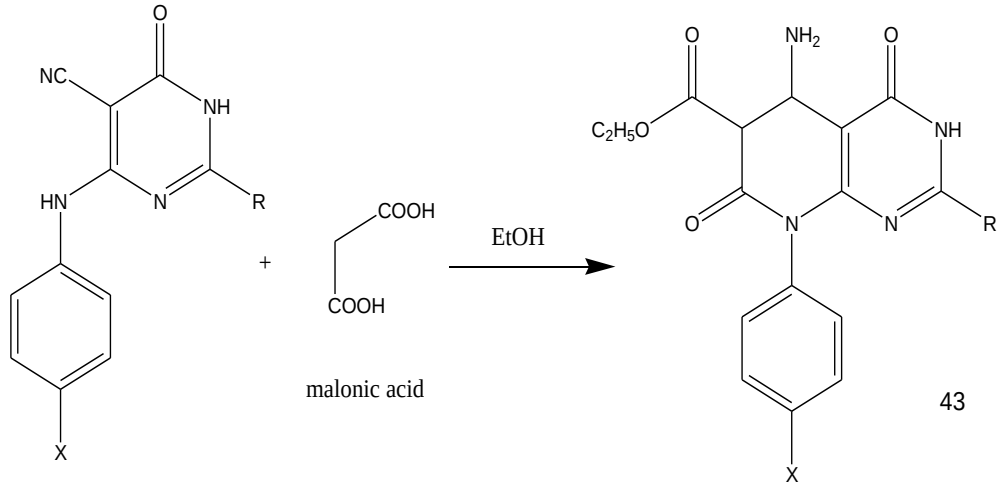
41

- (*E*)-3-(Benzenesulfonyl)-2-(methylsulfanyl) pyrido-[1, 2-*a*] pyrimidin-4-ylidenamine **42** was identified by **Wu et al., (2003)** as a potent and selective 5-HT6 antagonist, and a one-step synthesis has been developed for the same. This compound represents a distinct novel chemo type of 5-HT6 ligands and was expected to be a useful tool for further pharmacological evaluation of the function of the 5-HT6 receptors.



42

- Some novel Pyridopyrimidine carboxylate **43** derivatives were synthesized through nucleophilic substitution reactions with the use of amidines, followed by 4-haloanilines and malonic acid and were evaluated for antimicrobial and anticancer activity. The synthesized compounds A-F were characterized by UV, IR, ^{1}H NMR, mass and elemental analysis and were evaluated for their antimicrobial activity against B. subtilis, S. aureus, E. coli, S. typhi, Candida albicans and Aspergillus niger by disc diffusion method, anticancer activity against cancerous cells i.e. colon cancer (HT29), liver cancer (HepG2) and cervical cancer (Hela). All the compounds showed moderate to considerable antimicrobial and anticancer activity. **Verma et al., (2014).**



4-(4-halo phenyl amino)-2-substituted -6-oxo-1,6-dihydro pyrimidine-5-carbonitrile

ethyl 5-amino-8-(4-halophenyl)-2-substituted-4,7-dioxo-3,4,5,6,7,8-hexahydro[2,3-d] pyrimidine-6-carboxlate

MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1 GENERAL

Nuclear Magnetic Resonance (^{13}C-NMR) spectra were determined by Bruker Avance modern 400MHz NMR instrument in d-DMSO, $CDCl_3$ & D2O as solvents with tetra methyl silane as the internal reference. Chemical shift were quoted in parts per million (ppm).

The mass spectra was recorded using Jeol GC-mate –II spectrophotometer.

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^{0}C); ethyl acetate; ethyl alcohol were used as the developing solvents. Spots were detected with iodine.

The solvents and reagents used for the synthesis were of reagent grade and were purified by standard methods.

Chemdraw ultra10 was used to predict the ^{13}C NMR of the synthesised compounds.

3.2 PREPARATION OF AMIDE

3.2.1 Preparation of 5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid (46a)

2.5mM of 2-Amino 3-Methyl Pyridine was taken in the beaker and then added 2.5mM of glutaric anhydride. To this added, 10ml of alcohol. Then the above mixture was stirred for 30 minutes in a magnetic stirrer. The solid precipitated was collected and recrystallised from Ethyl alcohol.

3.2.2 Preparation of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid (46b)

2.5mM of 2-Amino 6-Methyl Pyridine was taken in the beaker and then added 2.5mM of glutaric anhydride. To this added, 10ml of alcohol. Then the above mixture was stirred for 30 minutes in a magnetic stirrer. The solid precipitated was collected and recrystallised from Ethyl alcohol.

3.2.3 Preparation of 5-(5-bromopyridine-2-ylamine)-5-oxopentanoic acid (46c)

2.5mM of 2-Amino 5-Bromo Pyridine was taken in the beaker and then added 2.5mM of glutaric anhydride. To this added, 10ml of alcohol. Then the above mixture was stirred for 30 minutes in a magnetic stirrer. The solid precipitated was collected and recrystallised from Ethyl alcohol.

3.3 CYCLISATION OF AMIDE USING PTSA

3.3.1 Preparation of 1-acetyl-9-methyl-1h-pyrido [1, 2-a] pyrimidin-4(9aH)-one (47a)

2.5mM of 5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid **(46a)** was taken in the 25ml round bottomed flask. To this added 50mg of PTSA. Then 10ml of alcohol was added and the mixture was kept for reflux in a water bath for 4 hours. The reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled and then poured in to 10ml of water, in the beaker. The solution was extracted with dichloromethane. The organic layer was separated dried over sodium sulphate. The evaporation of the solvent yielded the dirty white crystals. This was recrystallised with acetone to get pure white crystals.

3.3.2 Preparation of 1-acetyl-6-methyl-1h-pyrido[1,2-a]pyrimidin-4(9aH)-one (47b)

2.5mM of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid **(46b)** was taken in the 25ml round bottomed flask. To this added 50mg of PTSA. Then 10ml of alcohol was added and the mixture was kept for reflux in a water bath for 4 hours. The reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled and then poured in to 10ml of water, in the beaker. The solution was extracted with dichloromethane. The organic layer was separated dried over sodium sulphate. The evaporation of the solvent yielded the dirty white crystals. This was recrystallised with acetone to get pure white crystals.

3.3.3 Preparation of 1-acetyl-7-bromo-1h-pyrido[1,2-a]pyrimidin-4(9aH)-one (46c)

2.5mM of 5-(5-bromopyridine-2-ylamine)-5-oxopentanoic acid **(46c)** was taken in the 25ml round bottomed flask. To this added 50mg of PTSA. Then 10ml of alcohol was added and the mixture was kept for reflux in a water bath for 4 hours. The reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled and then poured in to 10ml of water, in the beaker. The solution was extracted with dichloromethane. The organic layer was separated dried over sodium sulphate. The evaporation of the solvent yielded the dirty white crystals. This was recrystallised with acetone to get pure white crystals.

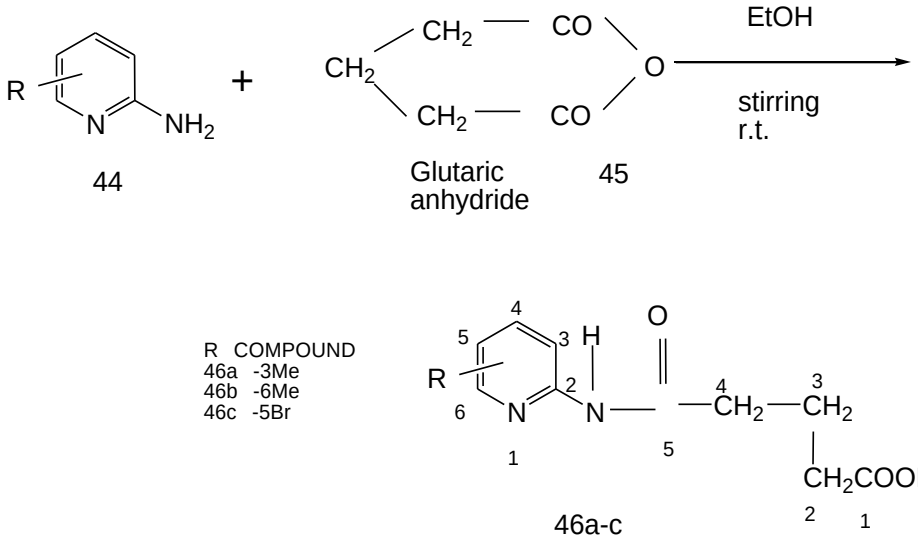
RESULTS AND DISCUSSION

4. RESULT AND DISCUSSION

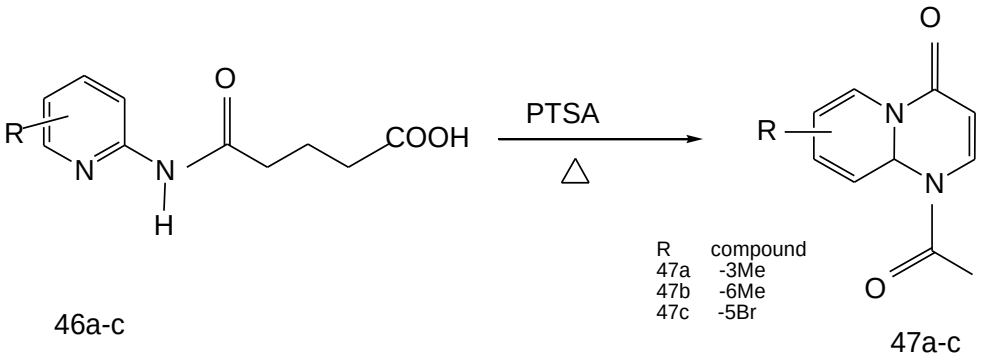
^{1}H and ^{13}C NMR is a powerful tool for the determination of structure of organic compound. ^{13}C chemical shifts are imperative part of NMR spectra, providing valuable, structural interpretation, molecular carbon skeleton and conformational variations of the compound. Hence in the present work structural analysis of compounds 5-(pyridine-2-ylamino)-5-oxo pentanoic acid and 1-acetyl-7-bromo-1H-pyrido[1,2-a] pyrimidin-4(9aH)-one were done using ^{13}C NMR and Mass spectrum.

The compounds 5-(pyridine-2-ylamine)-5-oxopentanoic acid **46a-c** and 1-acetyl -1H-pyrido [1, 2-a] pyrimidin-4(9AH)-one **47a-c** were prepared according to the procedure reported by **(Priyanka, 2015), [Scheme-I and Scheme-II].**

Scheme-1



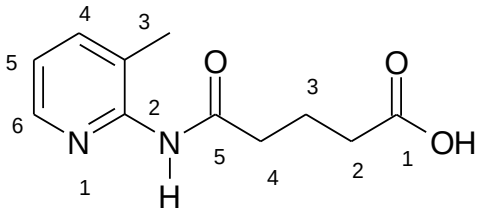
Scheme-2



46a-c

47a-c

4. 1 ^{13}C NMR STRUCTURAL ANALYSIS OF COMPOUND 46a



46a

5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid

Figure-1 gives the ^{13}C NMR chemical shifts.

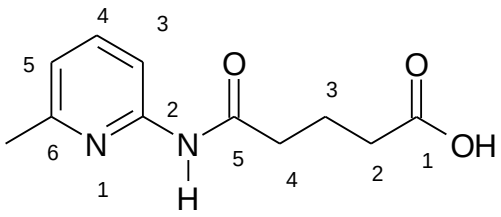
Totally there are eleven carbon atoms in the compound. The ^{13}C MNR spectrum of compound **46a** displayed nine sharp signals, for 9 carbon atoms.

- The signals at δ16.97 was assigned to Methyl group of the ring
- The signals at δ19.97 and δ32.79 were assigned to the C_3 and C_4 of the pentanoic acid moiety respectively.
- The chemical shift of the amide carbonyl carbon (C_5) was observed on the more downfield region, at δ174.132
- The carbonyl carbon of the acid group (C_1) appeared at δ158.1
- The peak at δ144.76 was assigned to C_2 and C_6 of pyridine ring.
- The peaks at δ112, δ115, δ136 were assigned to C_5, C_3 and C_4 of the pyridine ring.

Thus the ^{13}C NMR was in good agreement with the proposed structure.

For the other two compounds the ^{13}C NMR values along with assignments were given in table 1 and 2 (**Figure 2 & 3**). A comparative study was also made (**Figure 4 & 5**) with the predicted ^{13}C NMR values using Chem. draw ultra 10.00. For compound **46a** there is no much deviation in the observed and predicted values, expect for C_3 of the pyridine ring which resonated at high field δ115 than the predicted value δ122. This is because of the shielding effect of methyl group of the C_4 carbon than expected.

Similar results were obtained for the other two compounds **46b, 46c,** without much difference on the δ values.



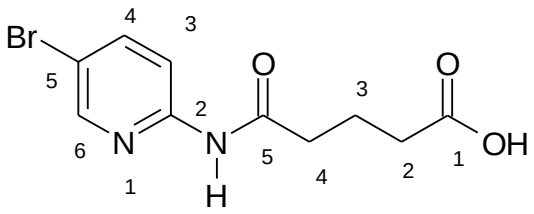
46b

5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid

TABLE - 1

^{13}C NMR SHIFT VALUES AND THEIR ASSIGNMENT FOR COMPOUND 46b

EXPERIMENTAL VALUE	PREDICTED VALUE	POSITION
18.23	20.4	Methyl group of pyridine ring
21.26	24.8	C_2 of acid
35.03	35.1	C_3 & C_4 of acid moiety
110.06	112.8	C_3 of the ring
112.54	120	C_5 of the ring
144.720	149	C_2 & C_4 ring
146.912	155	C_6 of the ring
154.032	173	C_1 (C=O) of acid moiety
180.509	177.3	C_5 (C=O) of acid moiety



46c

5-(5-bromopyridine-2-ylamine)-5-oxopentanoic acid

TABLE - 2

^{13}C NMR SHIFT VALUES AND THEIR ASSIGNMENT FOR COMPOUND 46c

EXPERIMENTAL VALUE	PREDICTED VALUE	POSITION
19.94	20.4	C_2 of acid moiety
32.74	35.1	C_3 & C_4 of acid moiety
105.03	117	C_3 of ring
109.967	111.1	C_5 of ring
139.157	147.5	C_2 & C_4 of ring
147.831	151	C_6 of ring
158.625	177	C_1 (C=O) of the acid moiety
174.042	173	C_5 (C=O) Of ring

4.2 STRUCTURAL ANALYSIS OF THE COMPOUND 47a

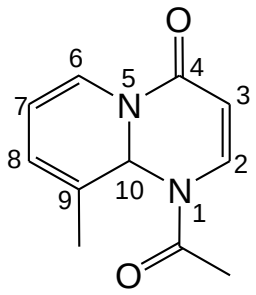
Figure 6 gives the 13C NMR of compound **47a**. The assignments of the carbon for the compounds **47a** were done on the basis of shielding and deshielding effects of nitrogen in the ring.

The carbon NMR spectrum of the compound displayed **47a** sharp singlets in the proton decoupled spectra which was in accordance with the structure proposed.

- The carbonyl group of the ring (C_4) position appeared at δ142.
- The other deshielded carbon, signal at δ154.4 was attributed to the 'C=O' of acetyl attached to the nitrogen ring.

- The CH_3 group of the pyrido ring attached to C_9 carbon, resonated at δ16
- The acetyl CH_3 group resonated at δ21.3
- The signal at δ141.6 was assigned to C_2 carbon
- The signal at δ112, δ123, δ125, δ128, δ132 were assigned to carbons C_{10}, C_3, C_7, C_8 and C_7 respectively.

Hence the ^{13}C NMR effectively favoured the proposed structure.

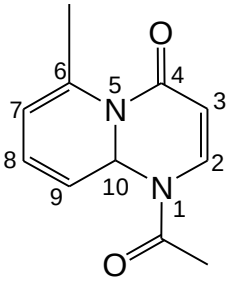


47a

1-acetyl-9-methyl-1h-pyrido [1, 2-a] pyrimidin-4(9aH)-one

Similar results were obtained for other compound also **47b &47c (Figure 7 & 8**). Table 3, 4 gives the ^{13}C NMR vales for compounds **47b & 47c** along with the assignments. In all the compounds C_2 carbon resonated at lower field because of the electro negativity of the nitrogen attached to it. Next C_6 carbon resonated at lower field, due to the anisotropy effect of C_4 carbonyl group. **(Hikmat. N Al. Jallo et al., 1978).**

A comparison (**Figure 9 & 10**) of the experimental ^{13}C values with the predicted ^{13}C NMR using Chem. draw was also done. There is no much deviation in the predicted and observed values.



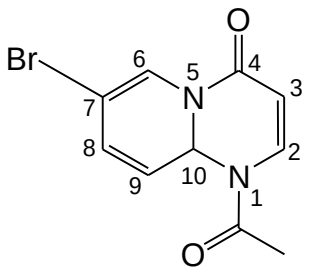
47b

1-acetyl-6-methyl-1h-pyrido[1,2-a]pyrimidin-4(9aH)-one

TABLE - 3

^{13}C NMR SHIFT VALUES AND THEIR ASSIGNMENT FOR COMPOUND 47b

EXPERIMENTAL VALUE	PREDICTED VALUE	POSITION
17.98	19.8	(CH_3) C_6
20.32	21.3	C_{12} (CH_3 of acetyl)
124.88	106.4	C_7
127.94	108.2	C_8
139.47	127.3	C_9
140.715	147.3	C_6
142.389	149.8	C_2
145.754	162.0	C_4
154.009	168.5	(C=O) C_{11} acetyl



47c

1-acetyl-7-bromo-1h-pyrido[1,2-a]pyrimidin-4(9H)-one

TABLE - 4

^{13}C NMR SHIFT VALUES AND THEIR ASSIGNMENT FOR COMPOUND 47c

EXPERIMENTAL VALUE	PREDICTED VALUE	POSITION
20.757	21.3	(CH_3 of acetyl) C_{11}
104.030	59.3	C_{10}
114.78	101.5	C_7
125.465	108.2	C_3
128.145	123.4	C_8
137.303	127.3	C_9
137.949	128.5	C_6
145.162	147.3	C_2
145.536	162.0	C_4
153.699	168.5	(C=O of acetyl) C_{11}

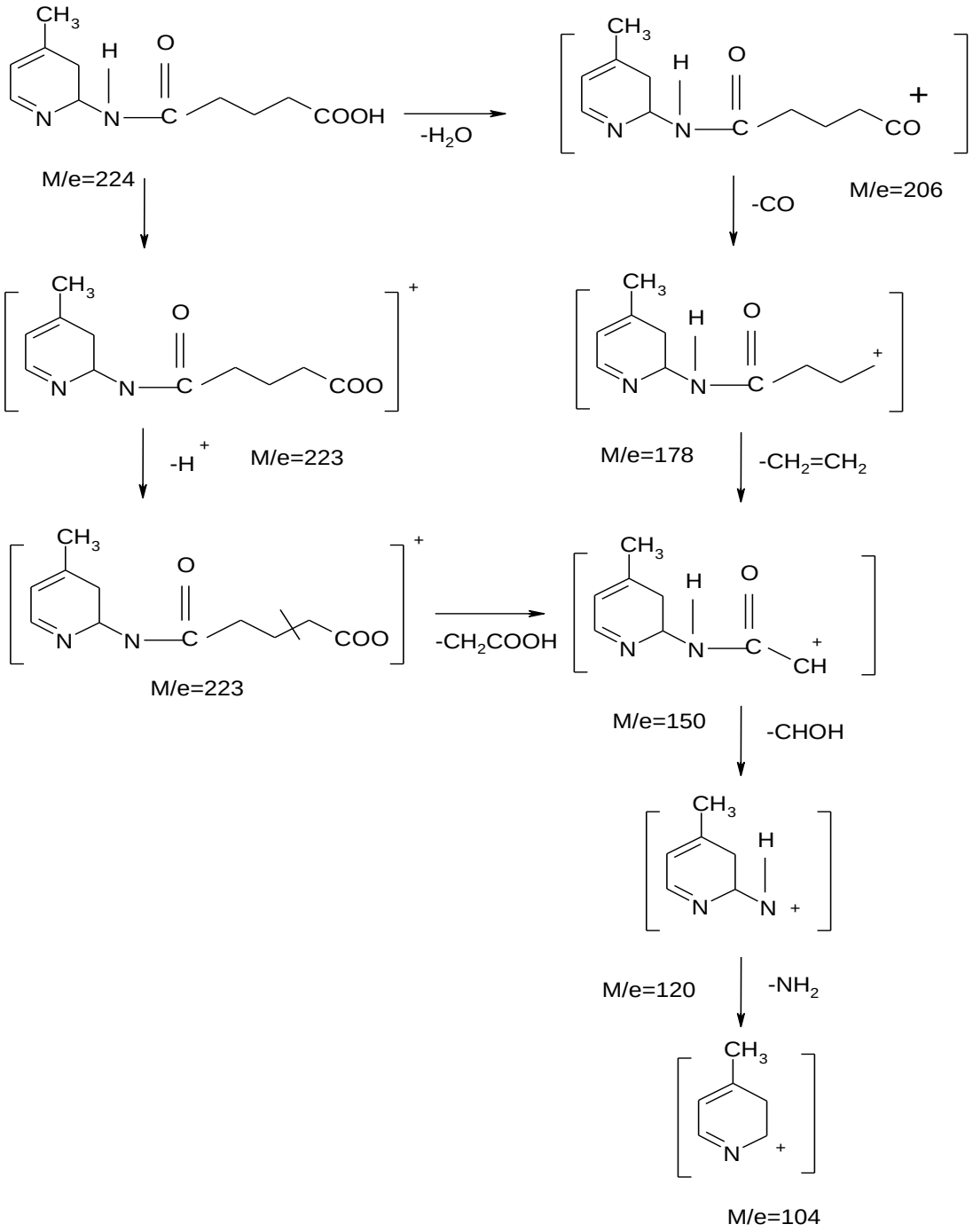
4.3 Mass spectral studies of compound 46b & 47b

A number of studies have demonstrated the utility of mass spectrometry in organic structure determinations. The method basically consists of the identification of modes of fragmentation where characterisation of certain structural features. In view of these mass spectral studies of the compound **46b & 47b** were carried out.

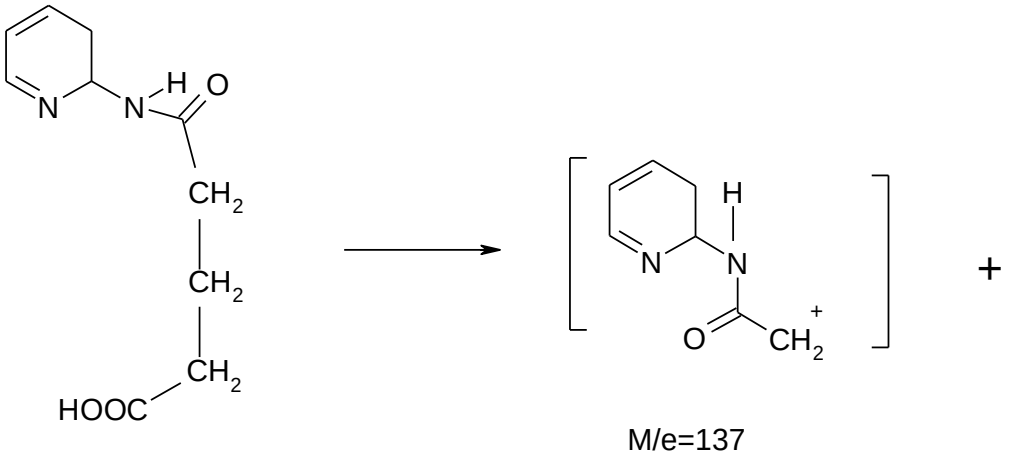
The mass spectrum of compound **46b & 47b** are shown in **Figure 11 & 12** and **scheme-3 & 4** gives the fragmentation pattern of **46b & 47b.** In both the cases the molecular ion peak not observable. Also the peaks obtained are of less intensity. In the case of **47b,** the low intensity may because of the initial cleavage of acetyl group is probably lower than the C_4 – N & C_2 & C_3 bond cleavage **(Ukrainets etal., 2007)**

Scheme - 3

Mass fragmentation pattern of 46b

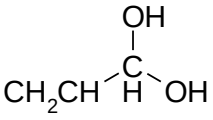


Mclafferty rearrangement



M/e=210

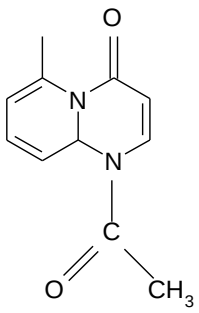
M/e=137



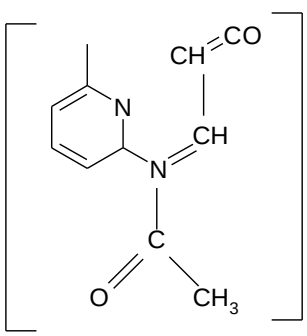
M/e=74

Scheme -4

Mass fragmentation pattern of 47b

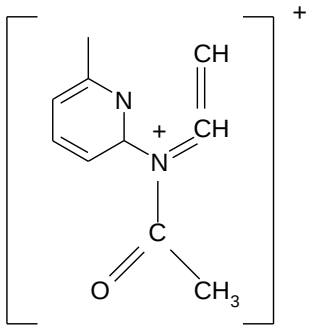


M/e=204

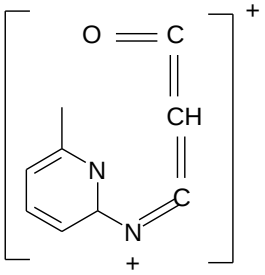


-CO

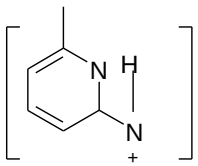
M/e=204



M/e=176

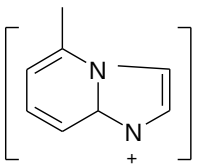


M/e=159



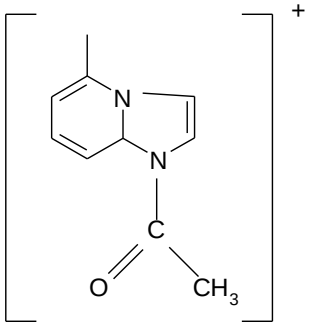
M/e=107

-NH

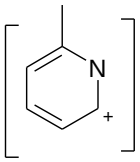


M/e=133

-$COCH_3$



M/e=176



M/e=92

Figure – 1: ^{13}C NMR OF 5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid

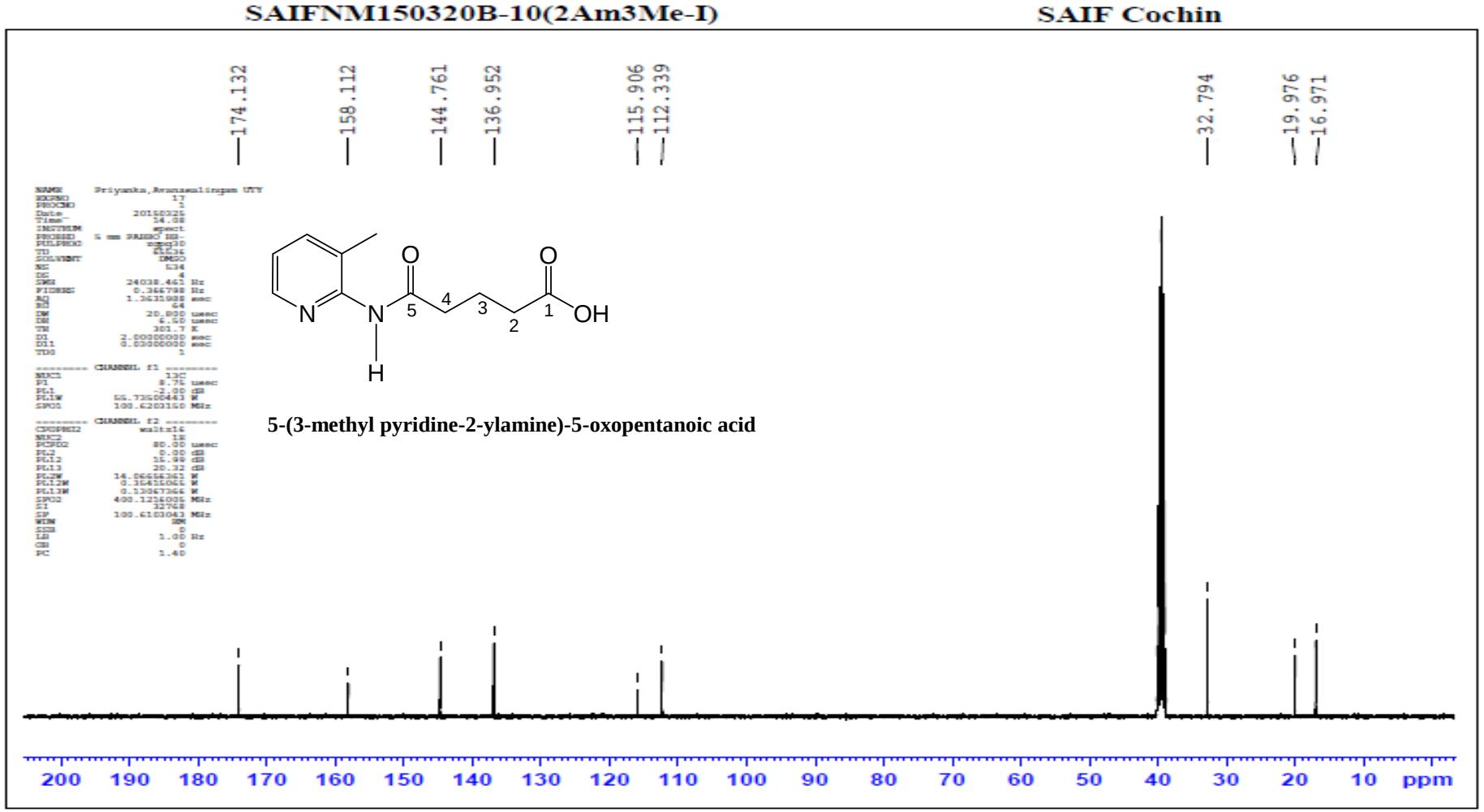


Figure – 2: ^{13}C NMR of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid

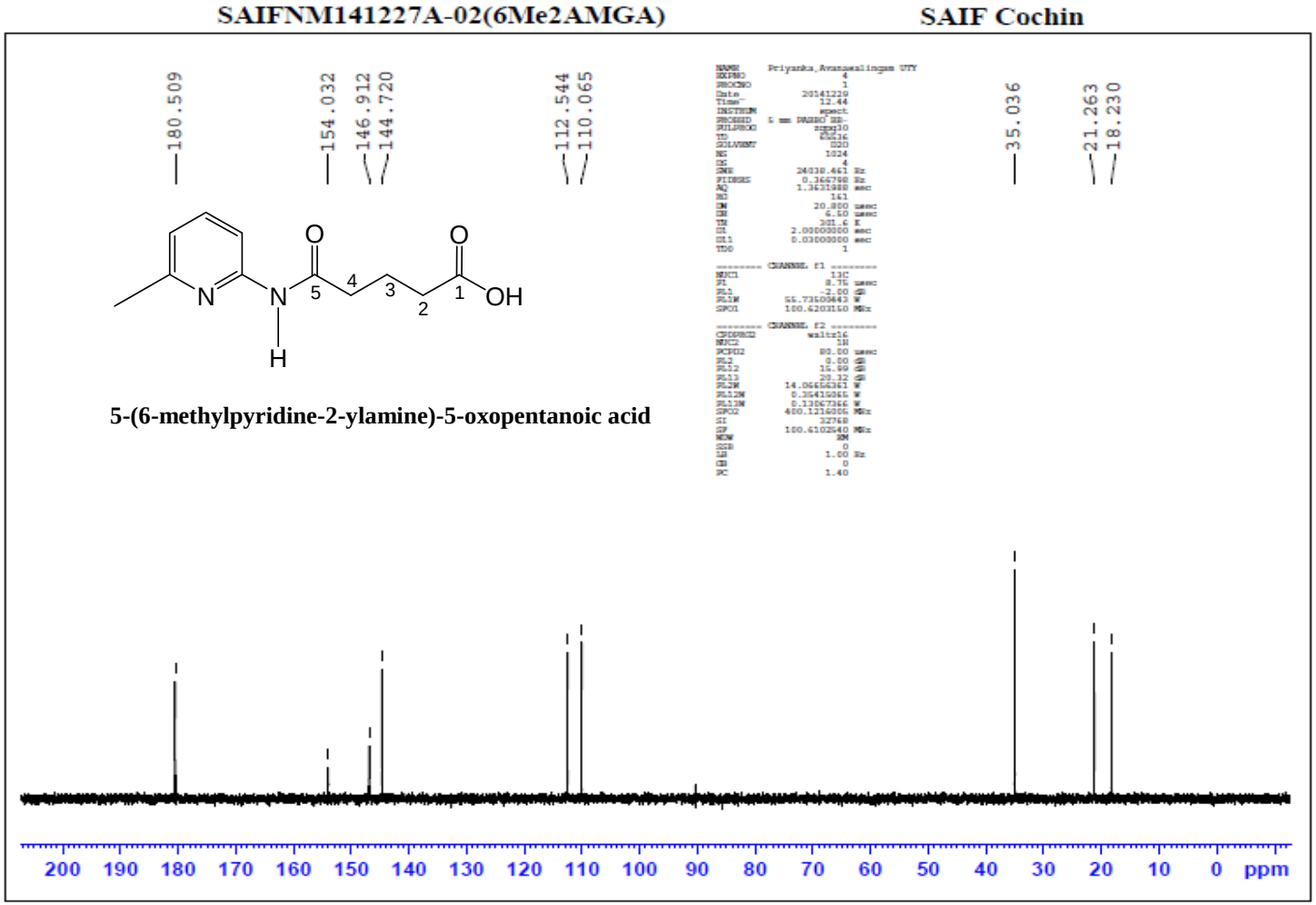
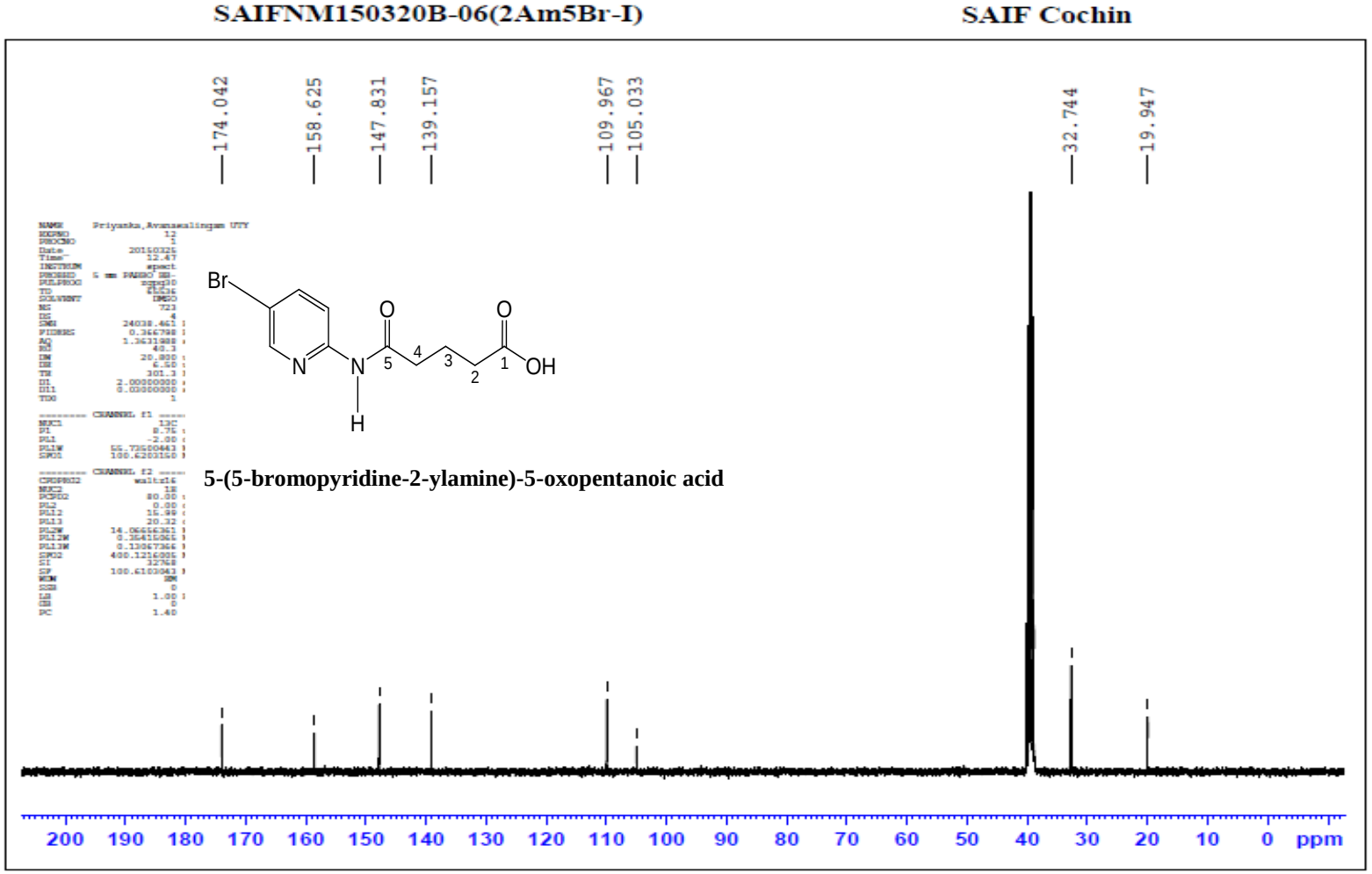


Figure - 3 : ^{13}C NMR of 5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid



5-(5-bromopyridine-2-ylamine)-5-oxopentanoic acid

Figure- 4

COMPARISION OF PREDICTED AND EXPERIMENTAL^{13} C VALUES FOR COMPOUND 5-(6-METHYLPYRIDINE-2-YLAMINE)-5-OXOPENTANOIC ACID

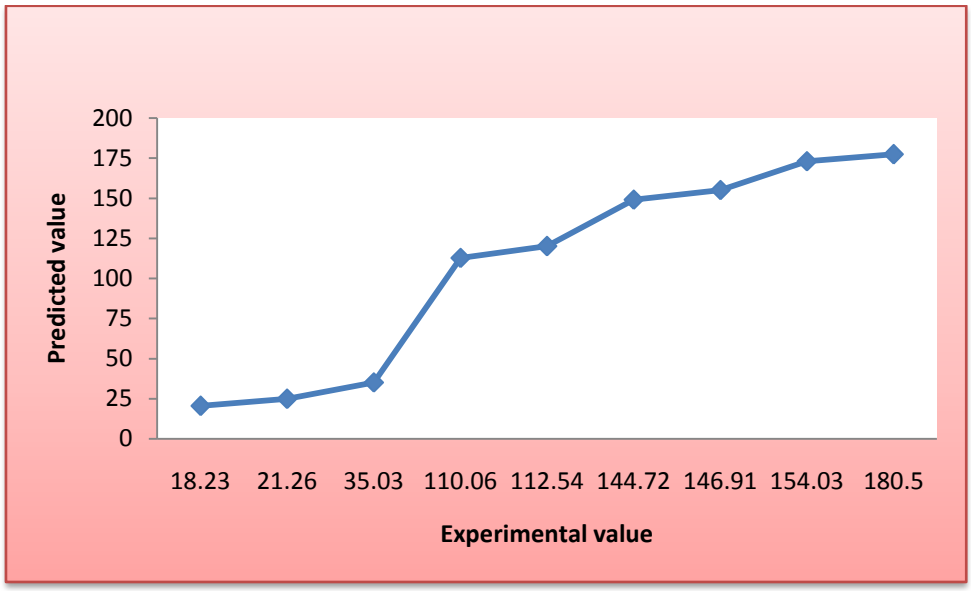


Figure- 5

COMPARISION OF PREDICTED AND EXPERIMENTAL^{13} C VALUES FOR COMPOUND 5-(5-BROMOPYRIDINE-2-YLAMINE)-5-OXOPENTANOIC ACID

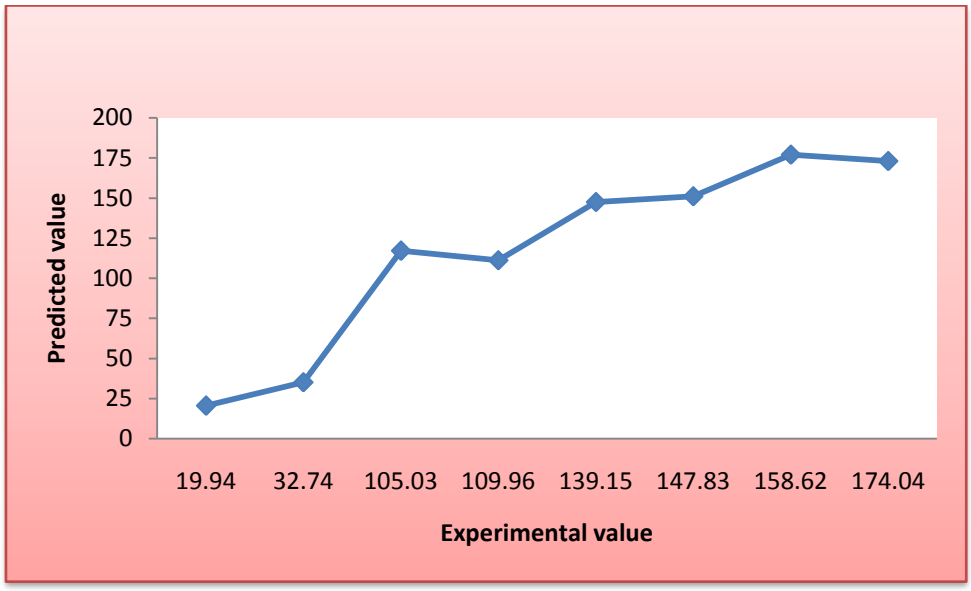


Figure -6: ^{13}C NMR of 1-acetyl-9-methyl-1H-pyrido [1, 2-a] pyrimidin-4(9aH)-one

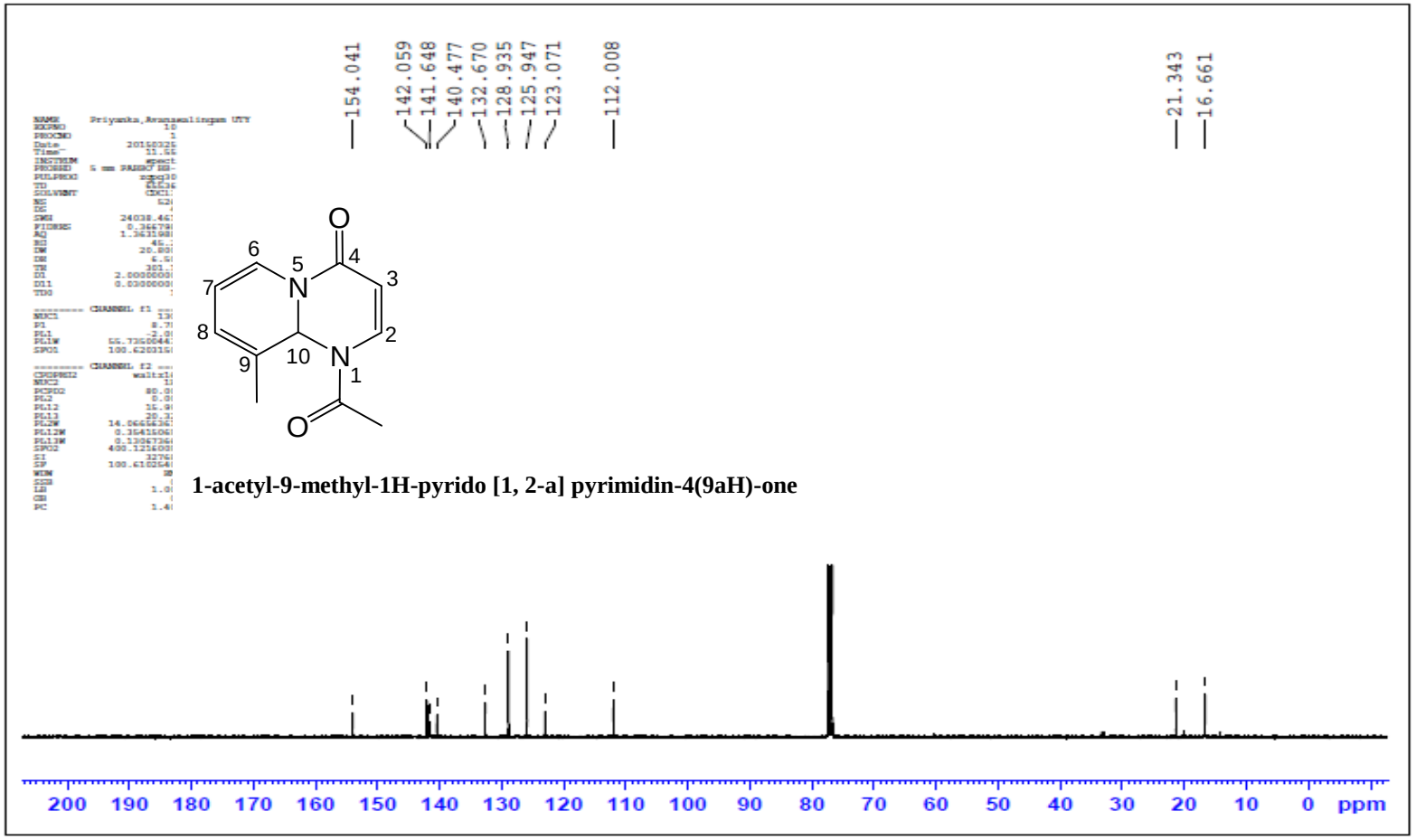


Figure – 7: ^{13}C NMR of 1-acetyl-6-methyl-1H-pyrido [1, 2-a] pyrimidin-4(9aH)-one

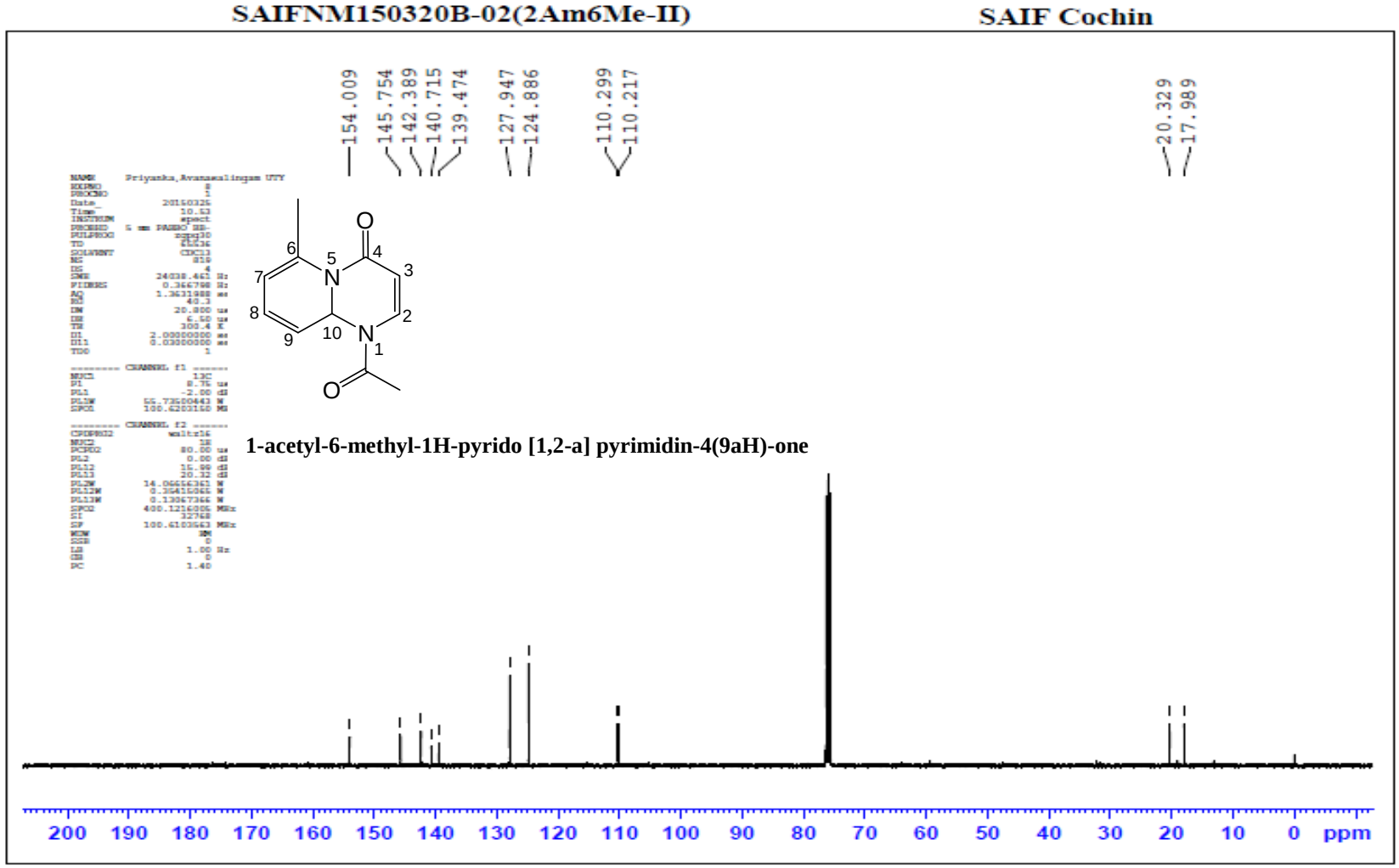


Figure – 8: ^{13}C NMR of 1-acetyl-7-bromo-1H-pyrido [1,2-a] pyrimidin-4 (9aH)-one

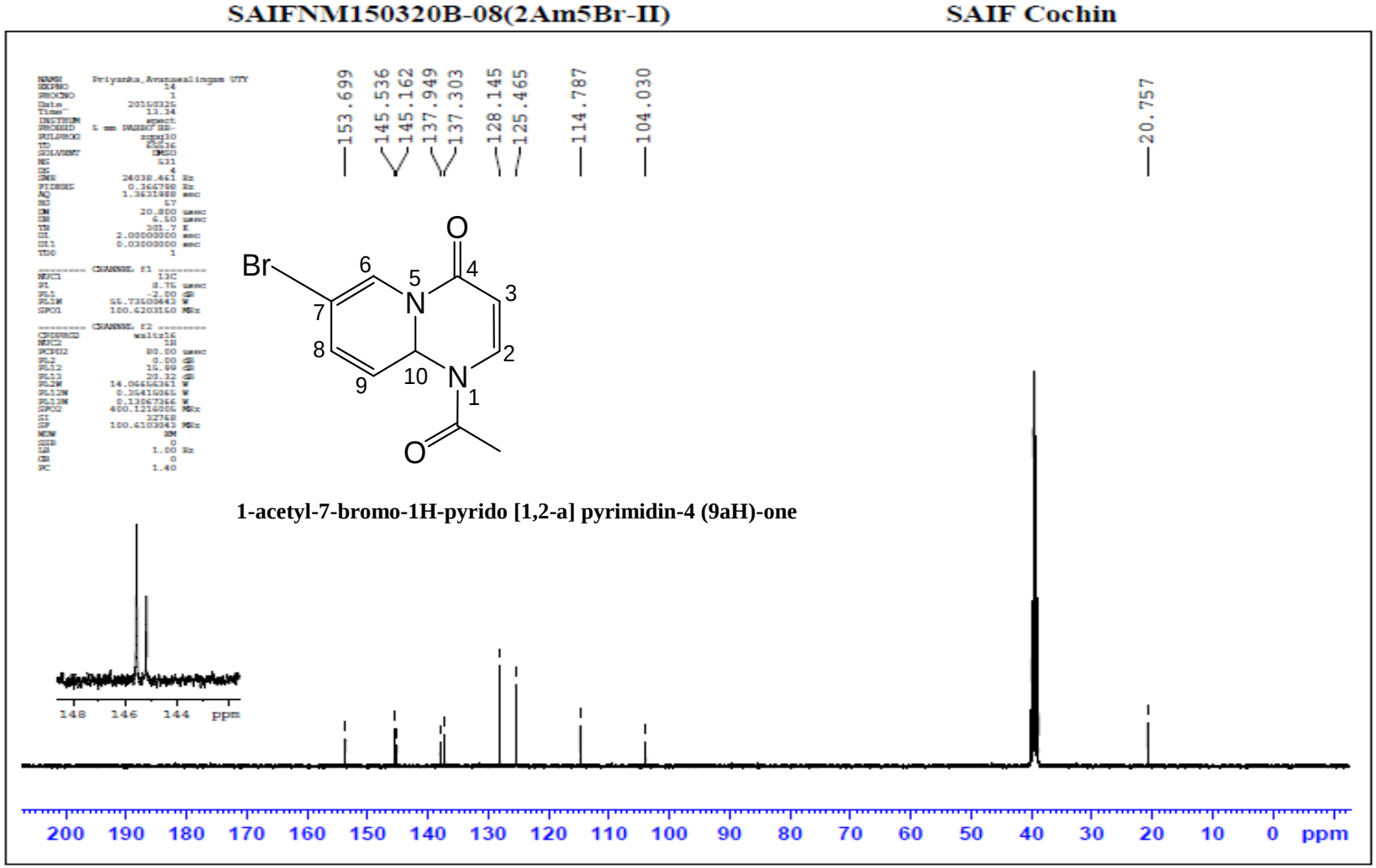


Figure - 9

COMPARISION OF PREDICTED AND EXPERIMENTAL^{13} C VALUES FOR COMPOUND 1-ACETYL-6-METHYL-1H-PYRIDO[1,2-A]PYRIMIDIN-4(9AH)-ONE

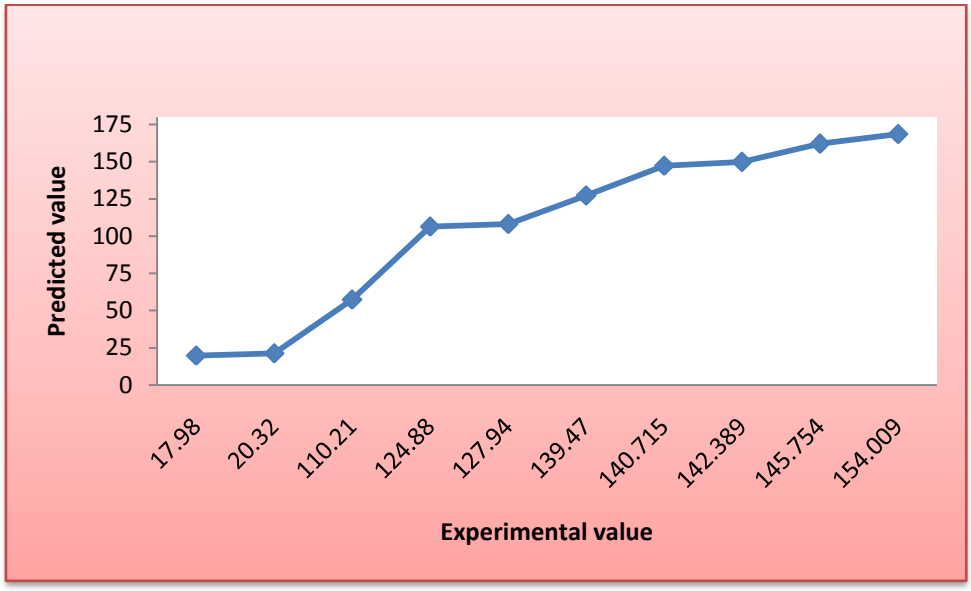


Figure - 10

COMPARISION OF PREDICTED AND EXPERIMENTAL^{13} C VALUES FOR COMPOUND 1-ACETYL-7-BROMO-1H-PYRIDO[1,2-A]PYRIMIDIN-4(9AH)-ONE

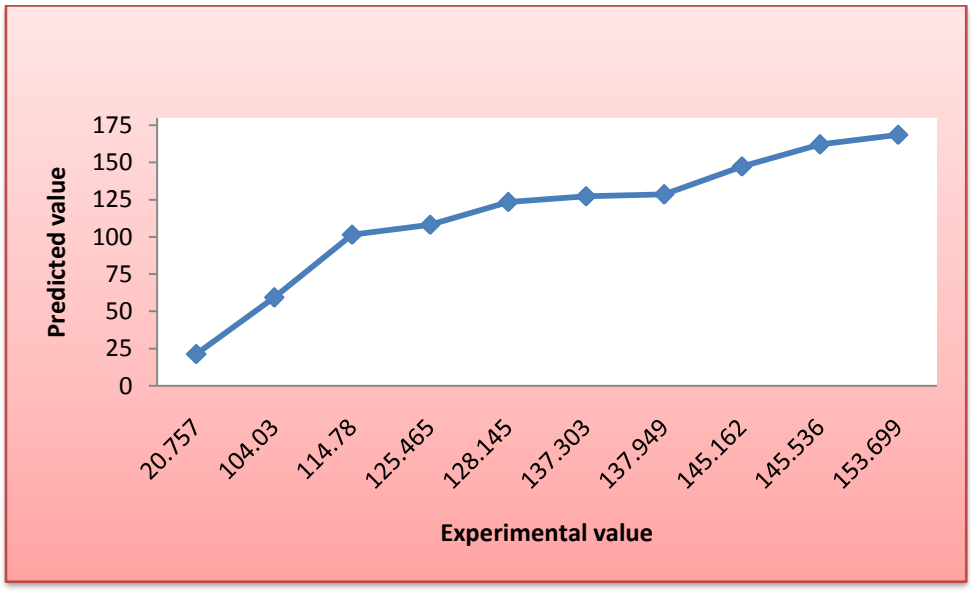


Figure -11: Mass Spectra of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid

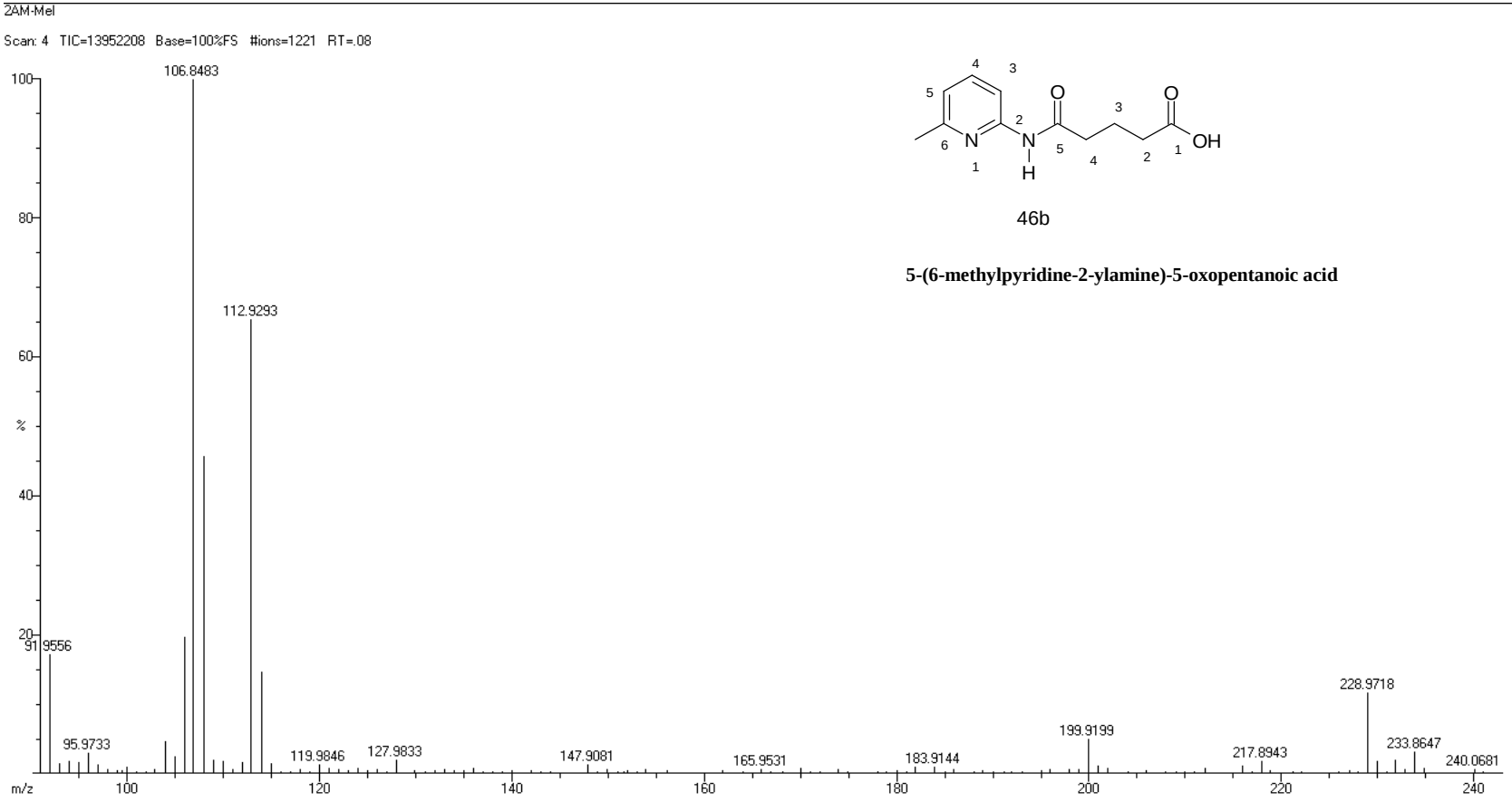
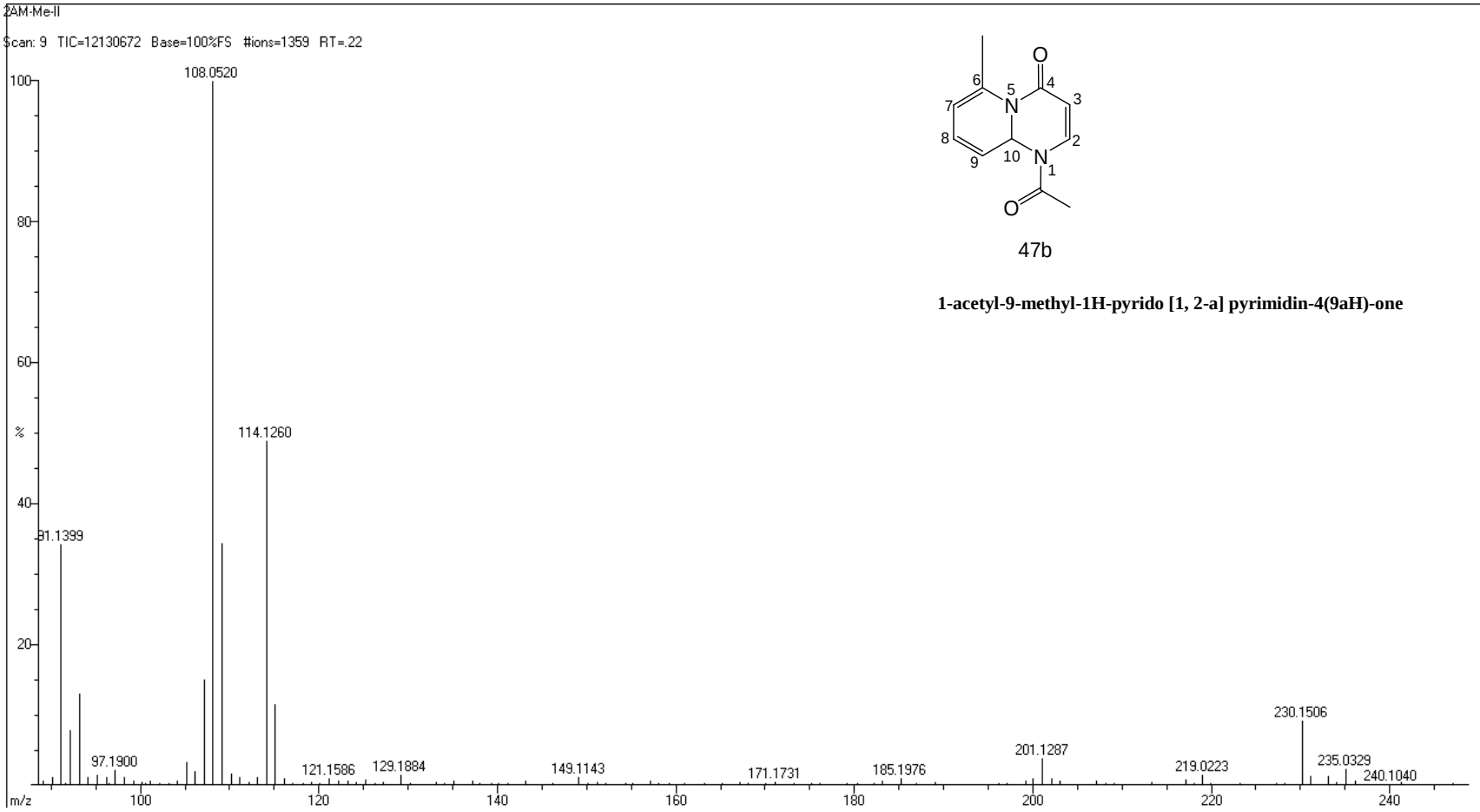


Figure – 12: Mass Spectra of 1-acetyl-9-methyl-1H-pyrido [1, 2-a] pyrimidin-4(9aH)-one



47b

1-acetyl-9-methyl-1H-pyrido [1, 2-a] pyrimidin-4(9aH)-one

SUMMARY AND CONCLUSION

5. SUMMARY AND CONCLSION

The findings of the 13C NMR and Mass Spectral studies of pyrido derivatives are summarized below

- ^{13}C NMR spectrum of compound 5-(pyridin-2-ylamino)-5-oxopentanoic acid displayed nine sets of signal.
- The predicted NMR values from Chem. draw ultra are in agreement with observed values.
- The C_3 carbon of the pyridine ring resonated at higher field at δ115 against the predicted value of δ122. This may be due to the more shielding effect from the methyl group attached to it.
- ^{13}C NMR spectrum of compound 1-acetyl-1H-pyrido [1, 2-a] pyrmidin-4(9aH)-one displayed eleven sets of signal.
- The comparison of predicted and observed ^{13}C values showed that there is much deviation in the values.
- The mass spectra were in accordance of the proposed structure. Hence the structure of the compounds 5-(pyridin-2-ylamino)-5-oxopentanoic acid and 1-acetyl-1H-pyrido [1, 2-a] pyrmidin-4(9aH)-one were unequivocally confirmed.
- The studies give an insight into the structural aspects of the compound. Further 2D studies can be carried out to study the conformational features of the compounds. Since structural and conformational aspects are important for the development of the molecule as a drug.

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