Reaction of 2-Amino pyridine with glutaric anhydride

By

PRIYANKA.D

REG NO: 13PCH012

A Dissertation submitted to

Avinashilingam Institute for Home Science and

Higher Education for Women University

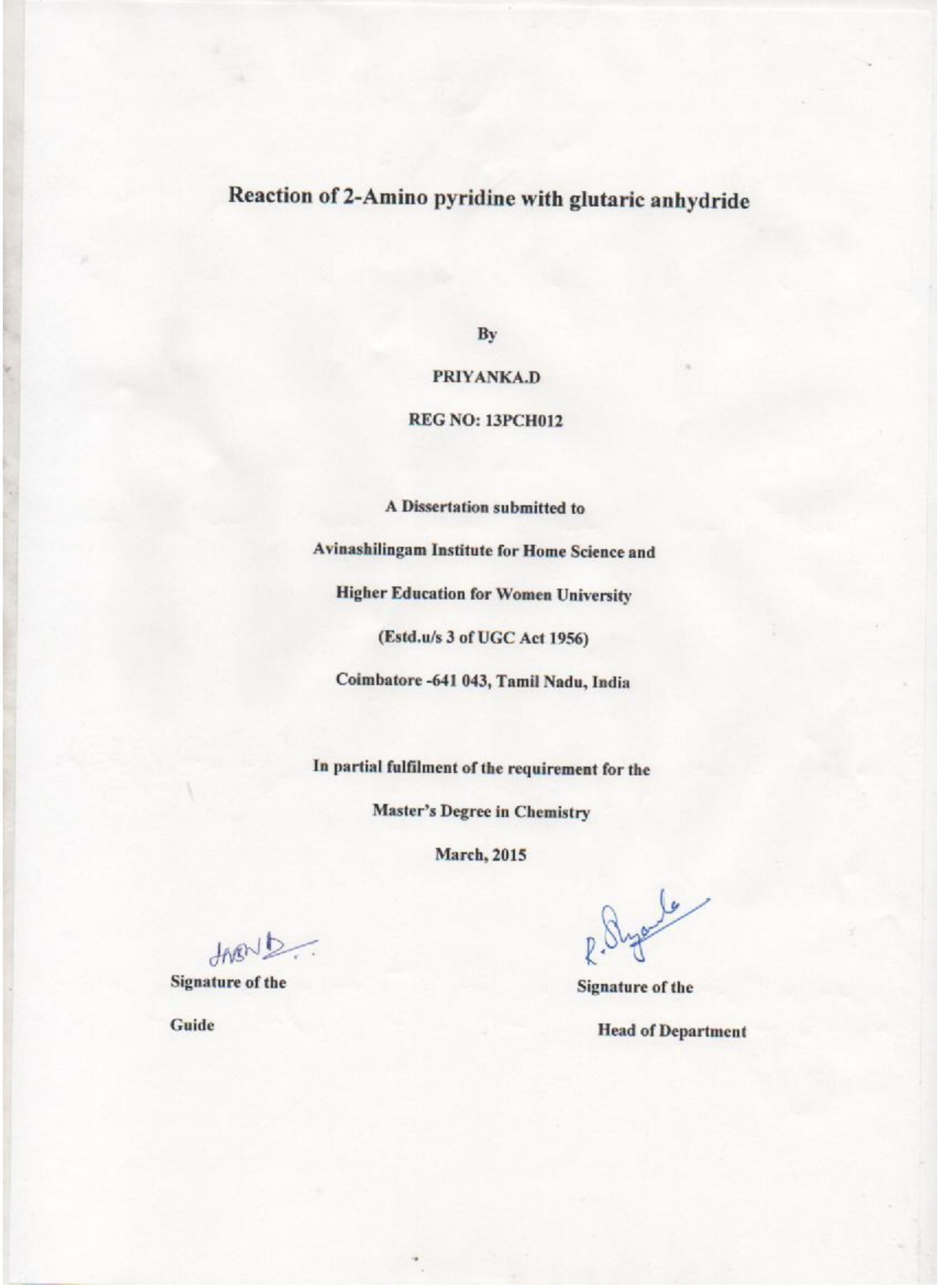
(Estd.u/s 3 of UGC Act 1956)

Coimbatore -641 043, Tamil Nadu, India

In partial fulfilment of the requirement for the

Master's Degree in Chemistry

March, 2015



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Signature of the
Guide

Signature of the
Head of Department

ACKNOWLEDGEMENT

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PRIYANKA. D

CONTENT

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LIST OF ABBREVIATIONS

NHC	-	Nitrogen Hetero Cycle
HDS	-	Hydro Desulphurization Process
ULSD	-	Ultra Low Sulphur Diesel
PCA	-	Passive Cutaneous Anaphylaxis
MCHPP	-	2-methyl-3-chloro-9-hydroxy-4H-pyrido[1,2a]pyrimidine-4-one
TsOH	-	Tosyl Hydroxide
PKM2	-	M2 Isoform Of Pyruvate Kinase
PI3K	-	Phosphoinositide – 3- Kinases
HIV	-	Human Immunedeficiency Virus
SAR	-	Structural Activity Relationship
DNA	-	Deoxyribo Nucleic Acid
DNA PK	-	DNA dependent Protein Kinase
NMR	-	Nuclear Magnetic Resonance
IR	-	Infrared
^{1}H-NMR	-	Proton Nuclear Magnetic Resonance
PTSA	-	Para Toluene Sulphonic Acid
DCM	-	Dichloromethane
EtOH	-	Ethanol
^{1}H-NMR	-	Proton 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 - Triethyl amine

DMF - Dimethyl Fluorine

NaN_3 - Sodiumnitrite

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

D_2O - Deuteriated water

$CDCl_3$ - Deuteriated chloroform

INTRODUCTION

1. INTRODUCTION

Cyclic compounds that have atoms at least two different elements as member of its rings are generally known as heterocyclic compound or ring structure. The branch of chemistry dealing with the synthesis, applications and properties of this heterocyclic compounds are known as hetero cyclic chemistry. **(Builla and Barluenga 2011)**

Most small heterocyclic compounds are non- or at least very weakly fluorescent and has many applications towards pharmaceuticals, also depending on the substitution pattern, they may have fungicidal activity or they may serve as inhibitors of 5-lipogenase.

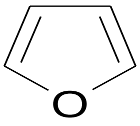
These hetero cyclic compounds play an important role in the drug discovery by the occurrence of a heterocyclic moiety in current drugs. **(Soural et al., 2008)**

The aromatic heterocyclic rings can be separated into basic aromatic rings and non-basic aromatic rings.

- In the **basic aromatic rings**, they can easily be protonated, and form aromatic cations and salts (e.g., pyridinium), the lone pair of electrons is not part of the aromatic system and extends in the plane of the ring. Examples of basic aromatic rings are pyridine or quinoline.

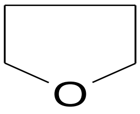
- In the **non-basic rings**, the lone pair of electrons of the nitrogen atom is delocalized and contributes to the aromatic pi electron system. In these compounds, the nitrogen atom is connected to a hydrogen atom. Examples of non-basic nitrogen-containing aromatic rings are pyrrole and indole.

Several rings contain basic as well as non-basic nitrogen atoms, e.g., imidazole and purine.



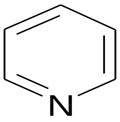
Furan

1



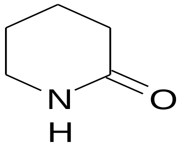
Tetrahydro
Furan

2



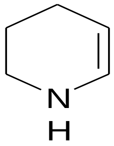
Pyridine

3



Piperidin-2-one

4



1,2,3,4-tetrahydro
pyridine

5

The **Nitrogen HeteroCycles** (NHC) are useful probes of competitive interactions because they may exist in either the neutral or cationic form over the typical range in groundwater pH and are important from an environmental health perspective. **(Zachara 1987)**

The enormous potential of N-heterocyclic carbenes(NHCs) as organo catalysts has become evident in recent years and plays an important role in the growing area of asymmetric organo catalysis. The phenomenal success of **NHCs** can be attributed primarily to their ability to invert the typical electrophilic nature of aldehydes (“umpolung”). (**Rafinski et al., 2014)**

The presence of hetero cyclic nitrogen compounds in diesel fuel inhibits the effectiveness of hydrodesulphurization process (HDS) even at low concentrations through competitive adsorption, causing coke formation, which leads to catalyst deactivation, making it a challenging for the oil refining industry to adhere to the increasingly stringent requirement to produce ultralow sulfur diesel (ULSD). **(Hizaddin et al., 2013)**

When pyridyl ring of 2, 2^1-bipyridine is substituted by a thiazolyl ring it leads to a highly fluorescent compound with the same structural motif for complexation. Depending on the substitution pattern, some interesting applications do exist as pharmaceuticals, fungicidal activity and also as inhibitors of 5-lipogenase. These substituted thiazoles are synthesized by cyclization from cysteine. (**Grummt et al., 2006)**

Ionizable N-containing aromatic hetero cyclic compounds like pyridine, quinoline, and acridine are used to evaluate competitive sorption in batch equilibrium experiments with two subsurface materials of different equilibrium pH in water. (**Zachara et al., 1987)**

The Stetter reaction is the most important umpolung processes which forms unique1, 4-dicarbonyl compounds and related derivatives, such as ketophosphonates, nitroketones, or ketonitriles. Various chiral **NHC**s have been developed, and the triazolium salts have proved to be the most efficient pre catalysts in numerous asymmetric applications. (**Rafinski et al., 2014**)

1.1 Nitrogen Bridgehead Compounds

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity. The interest in bicyclic 5–6 and 6–6 systems with one ring junction and one extra nitrogen atom stems from the saturated and partially saturated imidazo[1,2-*a*]pyridine and pyrido[1,2- *a*]pyrimidine ring systems in many biologically active compounds; some have pharmacological properties such as antiviral, antimalarial, antiulcer, analgesic, antiallergic, antiathmatic, and antipsychotic agents. **(ShujiangTu et al., 2007)**

The number of ring systems having bridgehead nitrogen atoms is small and considered to be less importance. Therefore, there are nearly eleven hundred such nuclei are considered to be important mainly in the dye stuff, pharmaceutical industries and in the study of natural products.

There are two major divisions were apparent in this bridge head nitrogen atoms:

- A – Valence bond bridged systems such aspyrrocoline etc.,
- B – Atom bridged systems such as quinuclidiene etc.

In this nine hundred ring systems were found to be in the category A and they have an homologues series as advantages, for example, pyrrole, indole, carbazole etc. in order to avoid the confusion, the ring systems were examined in the term “operative bicycle”, namely, the two ring systems sharing the bridgehead nitrogen atom(s).

1.2 Pyridopyrimidine Compounds

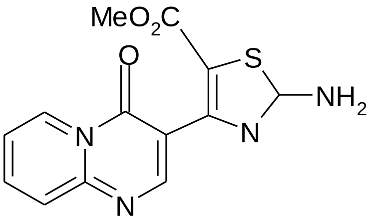
Pyridopyrimidines are bioactive nitrogen heterocyclic compounds and several of their substituted derivatives have been associated with diverse immune pharmacological activities such as analgesic, anti-inflammatory, anti-allergic, antiplatelet aggregator and anti-histaminic. **(Youssouf et al., 2008)**

The Pyridopyrimidine derivatives are used for treating or preventing a metabolic disorder, dyslipidemia, a cardiovascular disease, a neurological disorder, a hematological disease, cancer, inflammation, a respiratory disease, a gastroenterological disease, diabetes, a diabetic complication, obesity, an obesity-related disorder or non-alcoholic fatty liver disease.

The compound, 2-(3,4-dimethoxy phenyl)-3-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one, whose efficacy as a novel drug candidate for the treatment of vessel walls subjected to endovascular intervention has been studied by **Turco*et al.*, 2013**

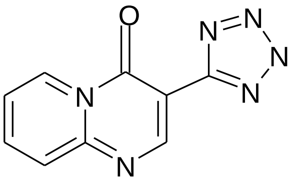
Many pyrido[1,2-a]pyrimidin-4-ones have been used for long time as medicines due to their high potencies and excellent efficiency in treatment of infections caused by different microbes. A literature survey showed that many 2-substituted 4H pyrido[1,2-a]pyrimidin-4-ones revealed potential antimicrobial activity and the novel derivatives showed antibacterial activity and was found to be comparable with nalidixic acid.

Many fused systems of pyrido[1,2-a]pyrimidin-4-ones were reported for their potential antimalarial effect and 9-Substituted 4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid revealed allergy inhibitory activity. Many derivatives of pyridopyrimidine like Risperidone, was explored and used in a wide range as potent antipsychotic agent. **(Abass*et al.*, 2009)**



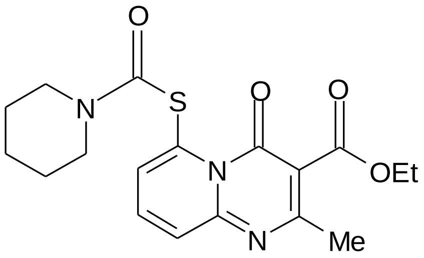
Azinopyrimidinone derivative

6



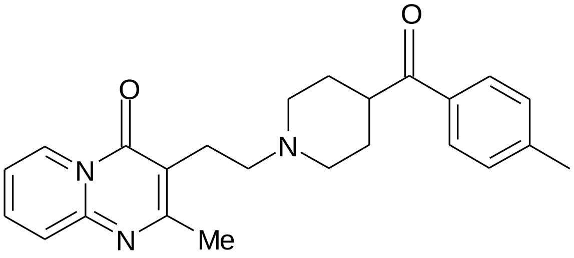
Pemirolast (antiasthmatic agent)

7



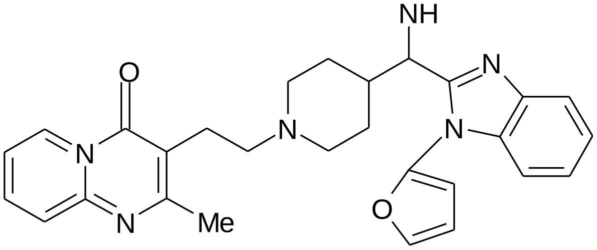
Antiulcerative agent

8



Pirenperone (Tranquilizer)

9



Barmastine (Antiallergic agent)

10

Examples of biologically active pyrido[1,2-a]pyrimidin-4-ones

1.3 Objectives

The main stimulating factor in the study of nitrogen heterocyles is the search for compounds of therapeutic importance. Pyrido[1,2 a] pyrimidine is one such compound exhibit vastrange of biological and pharmacological activity.Over the past few years the use of *p*-toluene-sulfonic acid (p-TsOH) as a catalyst has received considerable attention in different areas of organic synthesis **Reddy and Raghu(2008).**

In continuation of the work to develop environmentally benign Synthesis of pyrido[1,2-a] pyridine-4- ones, the present work aimed at,

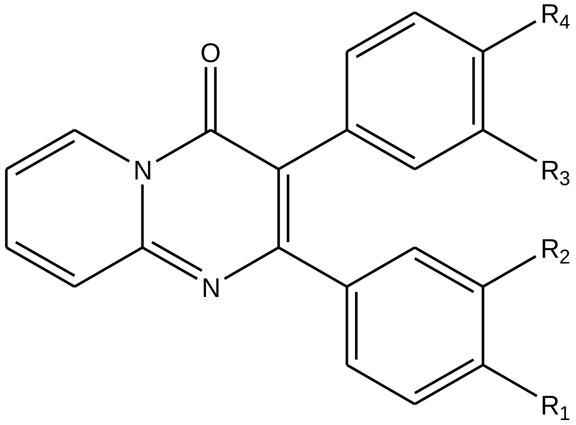
- Synthesis of pyrido [1,2-a] pyrimidin-4-ones by the reaction of 2-amino pyridine andglutaric anhydride.
- And the cyclization of amide formed into tyepyrido [1,2-a]pyrimidine using PTSA as catalyst.
- Characterization of the synthesized compounds by IR and H^1 NMR technique.

REVIEW OF LITERATURE

1. REVIEW OF LITERATURE

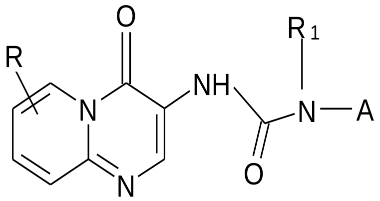
- 2,3-diphenyl-4H-pyrido[1,2-a]pyrimidin-4-one**(11)**derivative was examined by**Turco et al ., (2014)** as novel compounds for its effects in vitro on induced-cell proliferation and activation in human aortic smooth muscle cells (HAoSMCs) and in human umbilical vein endothelial cells (HUVECs). When 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.



11

- Novel pyrido[1,2-a]pyrimidin-4-ones**(12,13,14,15)** 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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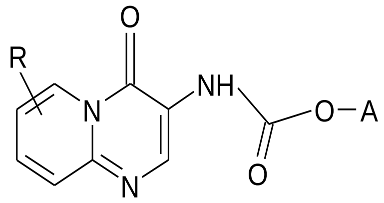

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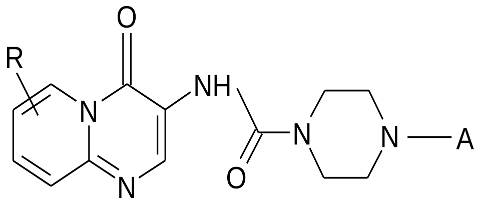

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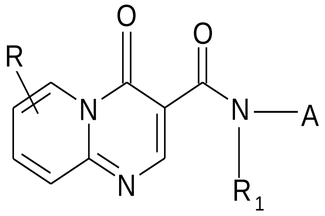

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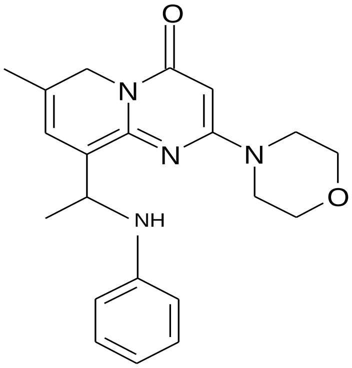
Where : R = H, 8-CH_3, 7-Cl, 4-C_6H_4OCH3
R1 = H, Alkyl
A = Allkyl / heteroaryl or alkyl

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**(16,17,18)** as PI3Kb/d inhibitors. Structure–activity relationships and structure–property relationships around the aniline and the amide substituents were studied.



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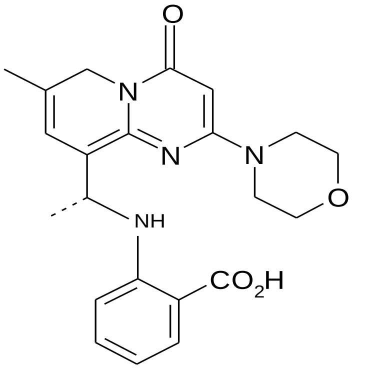

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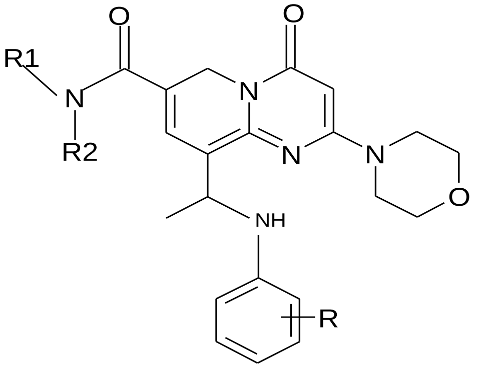

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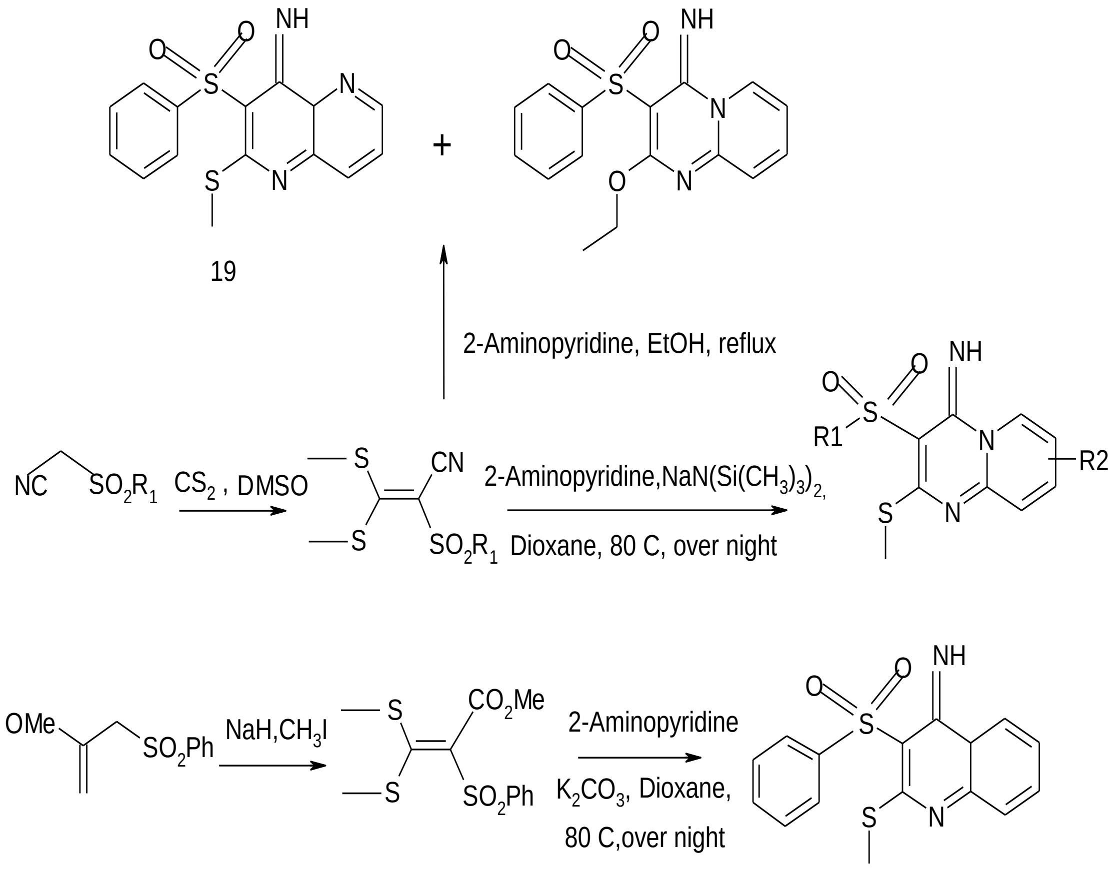
- **Shuanghua et al., (2014)** reported the synthesis of derivatives of 2-(methyl thio)-3-(phenyl sulfonyl)-4H-pyrido [1,2-a] pyrimidin-4-imine Structural solutions to the observed metabolic instability of (**19)** were identified using a human microsomal assay however, modifications that provided oxidative 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 **(19)**displayed good brain uptake in rats following intra-peritoneal administration, but limited oral bioavailability.



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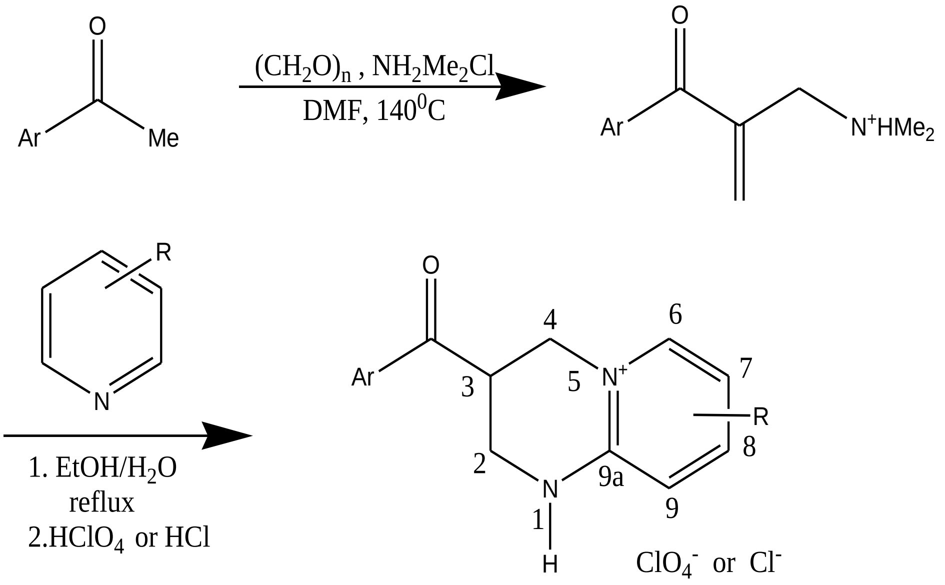
- 1,2,3,4-tetrahydro-pyrido[1,2-a]pyrimidinium perchlorates and chlorides**(20)**, with and without methyl substituent's in the unsaturated part of the heterocycle, were analysed by **Girreser et al ., (2013).**



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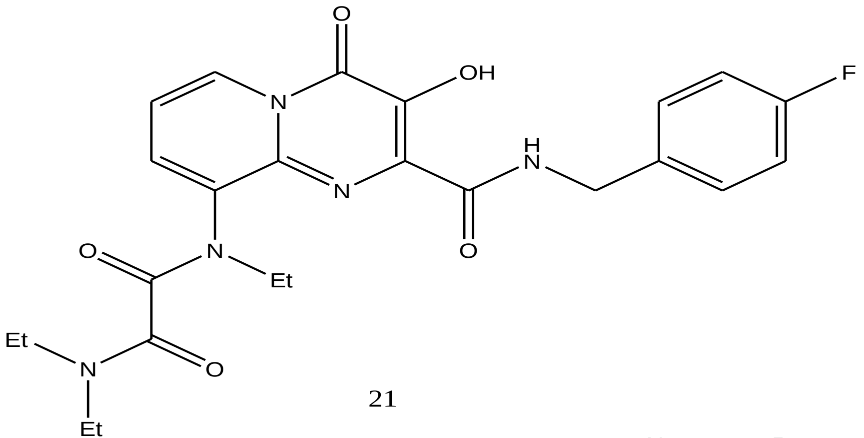
Data set of $_{1}{}^{1}$H, ^{13}C, ^{15}N and ^{35}Cl chemical shifts in DMSO-d6. ^{1}H, ^{13}C and ^{1}H, ^{15}N long range couplings were investigated in structure elucidation. The influence of the methyl substituents was analyzed on the proton, carbon and nitrogen shifts. A significant effect of the 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**(21, 22)** 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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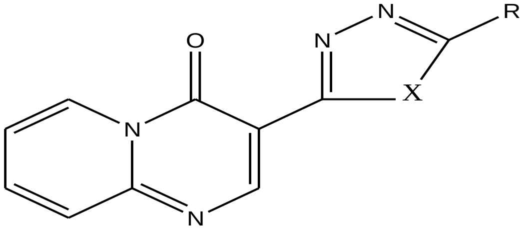
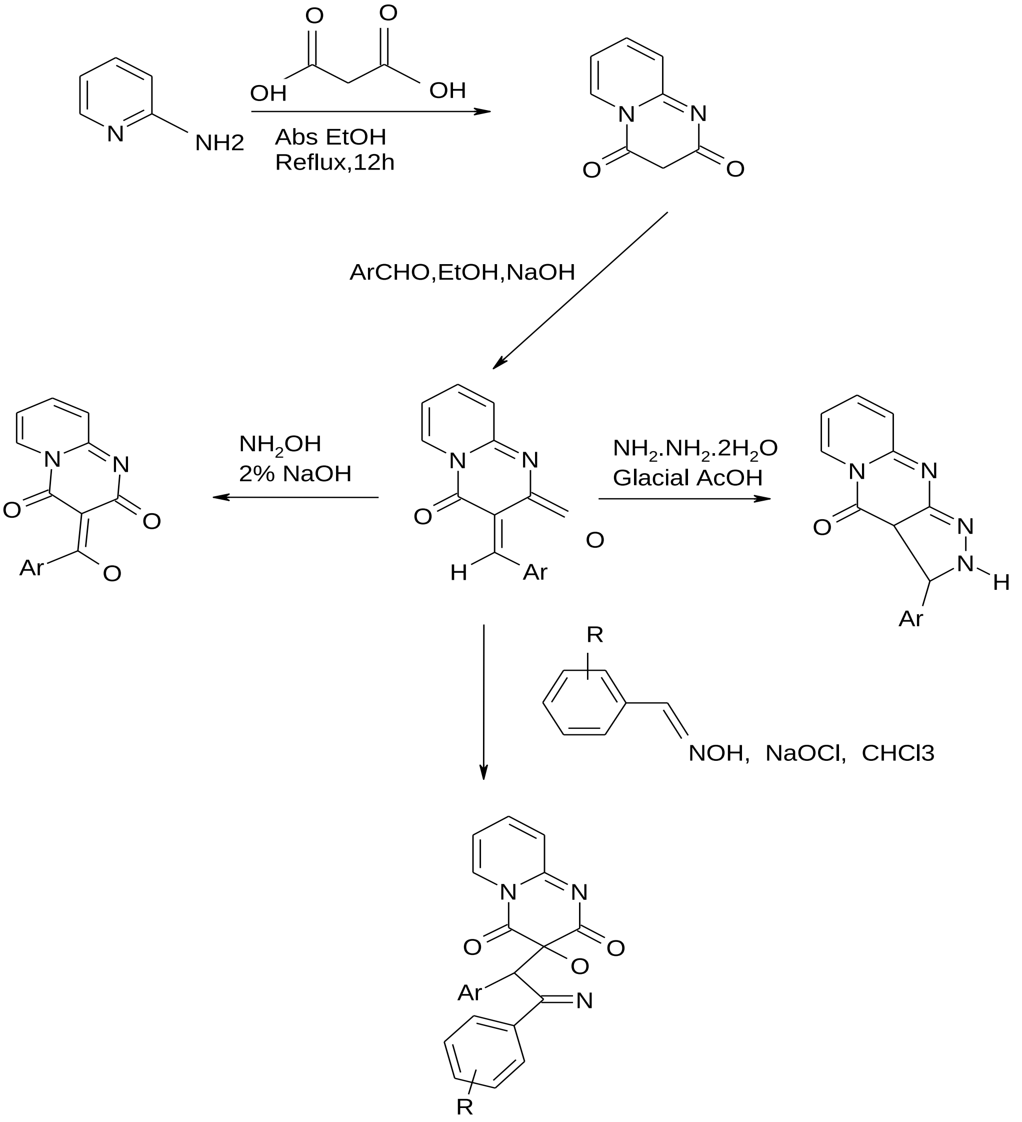


22

- **Bishnoi et al., (2013)**, developed a method for the synthesis of 4-(substituted phenyl)-3-(3-substituted phenyl)4*H*spiro[isoxazole-5,3_-pyrido[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**(23)**which consists of the conversion of 2*H*-pyrido[1,2-*a*]pyrimidine- 2,4(3*H*)-dioneto chalconesand 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.



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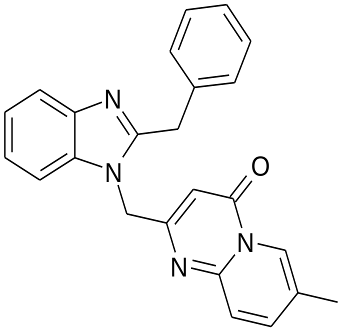
Synthetic route for cyclization products of 3-(4-substituted benzylidene)-2H-pyrido [1,2-a] pyrimidine 2,4-(3H)-diones.

- **Guo et al., (2013)** describe the 2-((1H-benzo[d]imidazol-1-yl) methyl)-4H-pyrido[1,2-a]pyrimidin-4-ones**(24-27)** 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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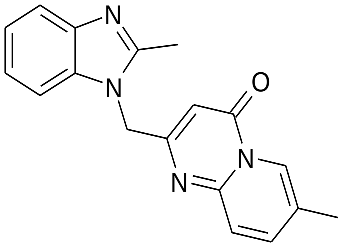

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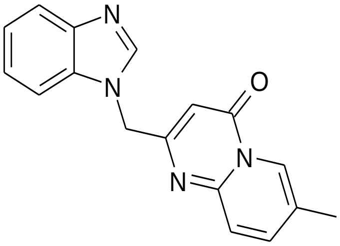

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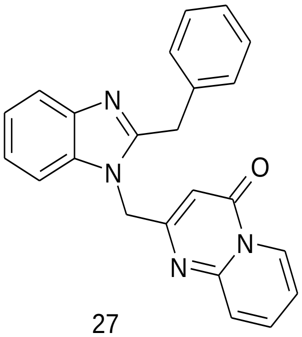
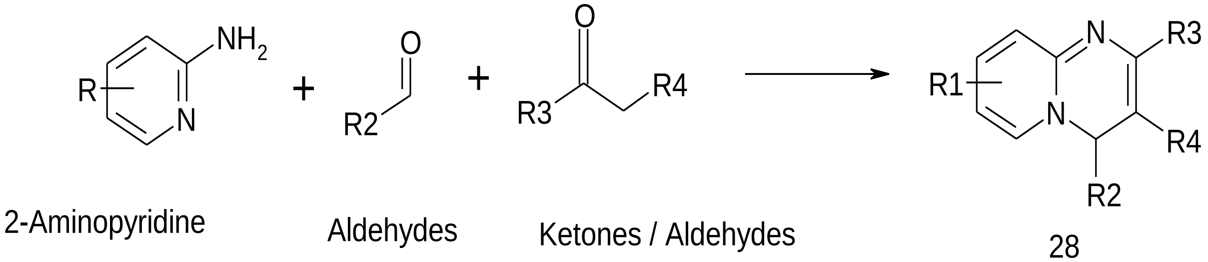


27

- 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**(28, 29)**.



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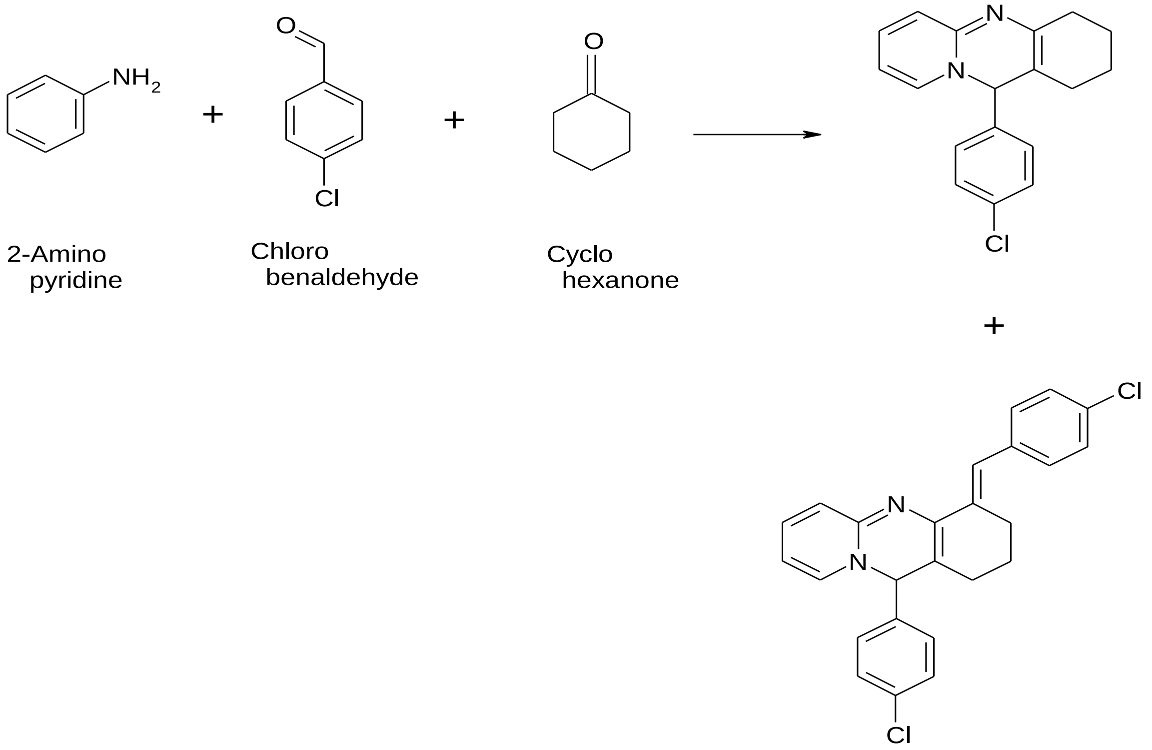
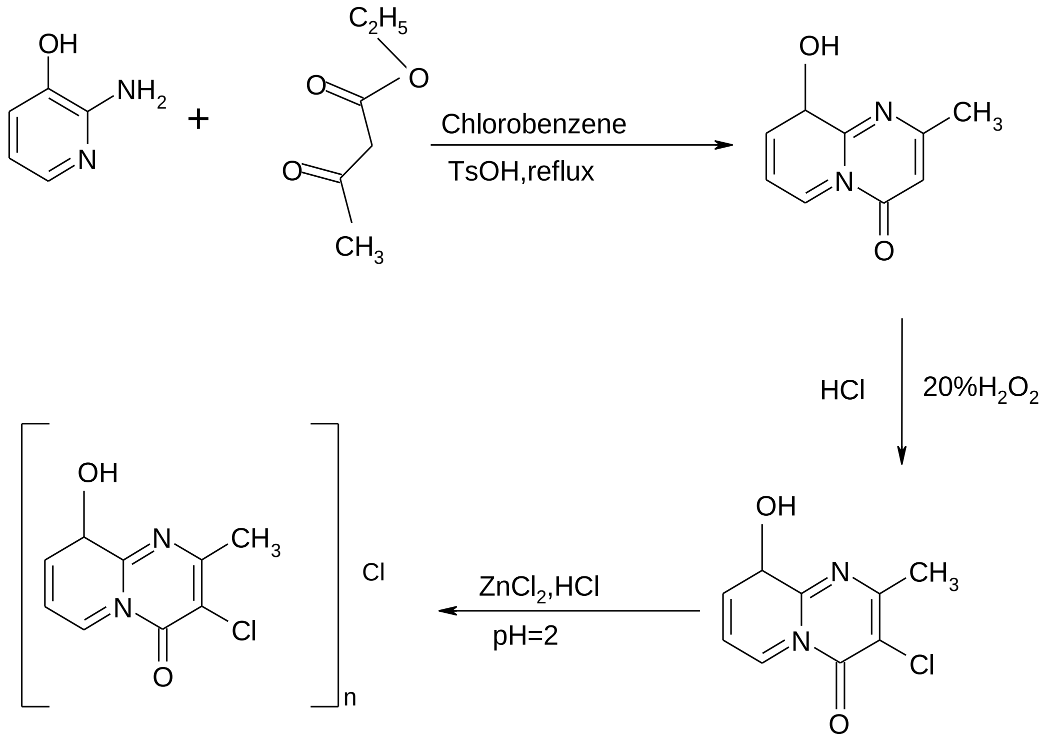


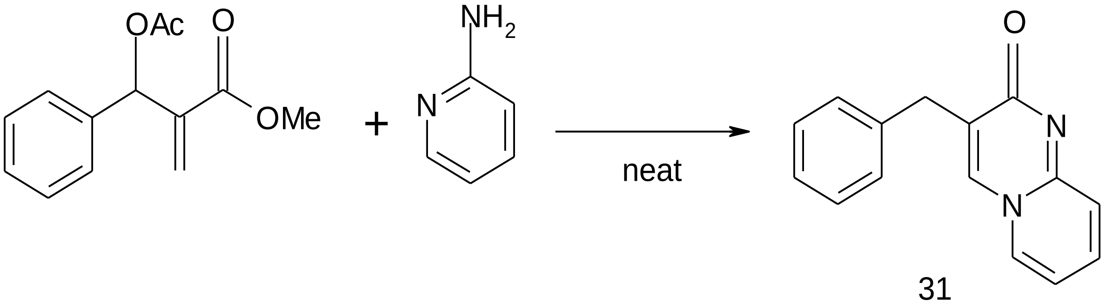
29

- A distinct compound, 2methyl-3chloro-9-hydroxy-4H-pyrido[1,2a]pyrimidine-4-one (MCHPP)**(30)**, has been prepared and characterized by **Zhang et al., (2013).** A study on the interaction of the title compound, 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.



30

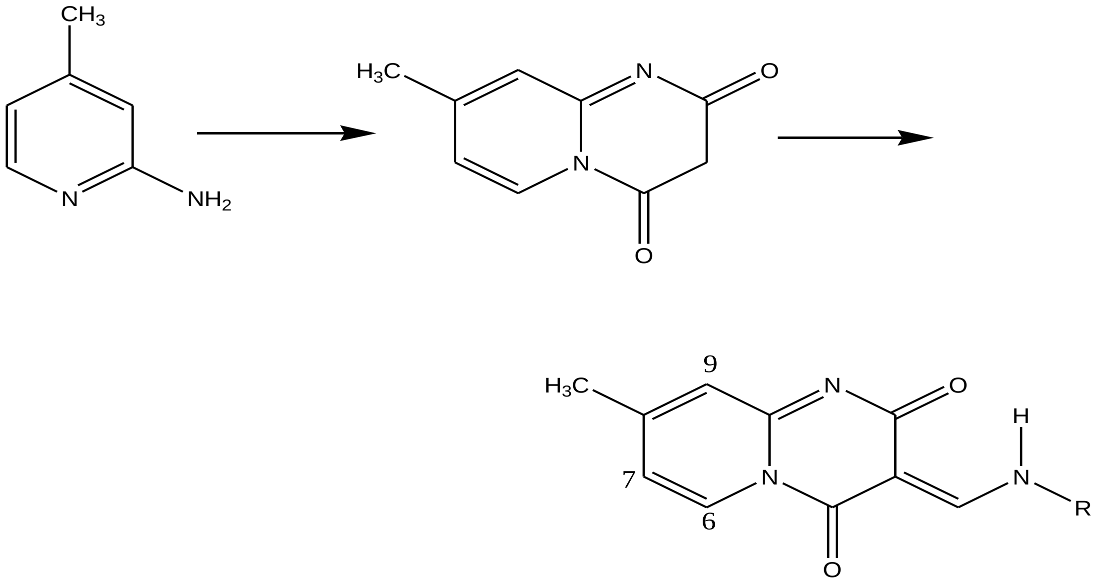
- A rapid synthesis of 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-one**(31)** derivatives by means of cyclocondensation of 2-(acetoxy(aryl)methyl)acrylates with 2-aminopyridines using microwave irradiation under neat condition was reported by **Satyanarayana et al.,(2013).** The major advantages of this reaction were,
    - reaction times
    - high conversions
    - catalyst and solvent-free conditions
    - Operational simplicity.



31

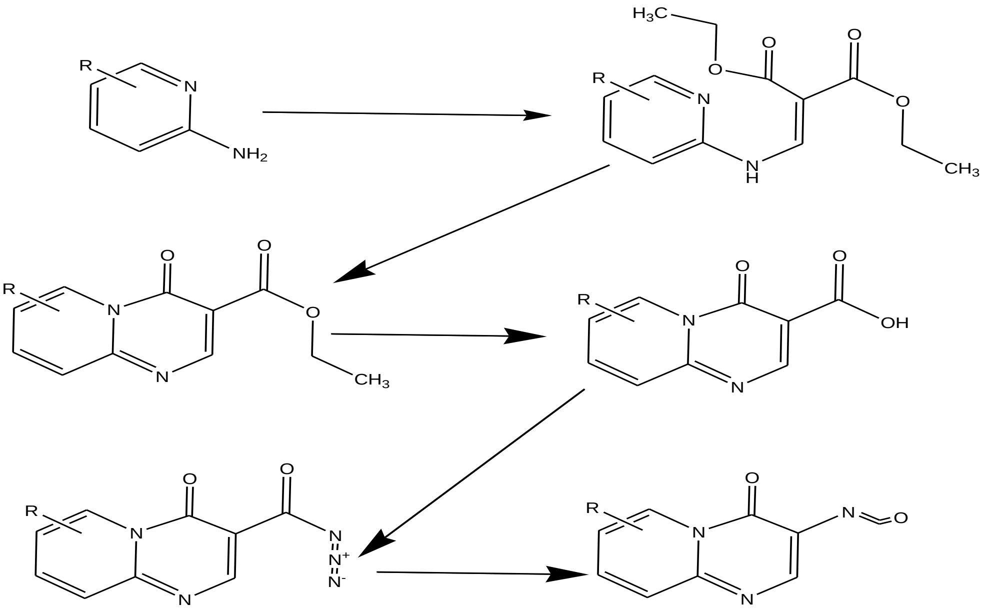
Reaction of Baylis - Hilman acetate with 2-aminopyridine

- 5-substituted-8-methyl-2H-pyrido[1,2-a]pyrimidine-2,4(3H)-diones**(32)**were reported by **Rauf et al ., (2012).** The chemical structures of all the compounds were elucidated by IR, ˋ 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 suggested 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.



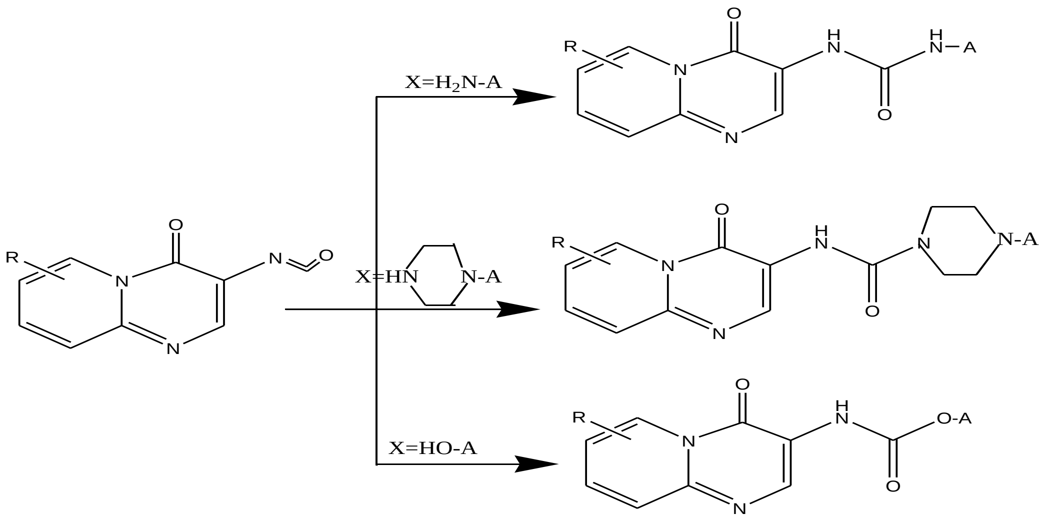
32

- Thirty two pyrido[1,2-a]pyrimidin-4-one derivatives**(33,34)**, 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).**



33

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.

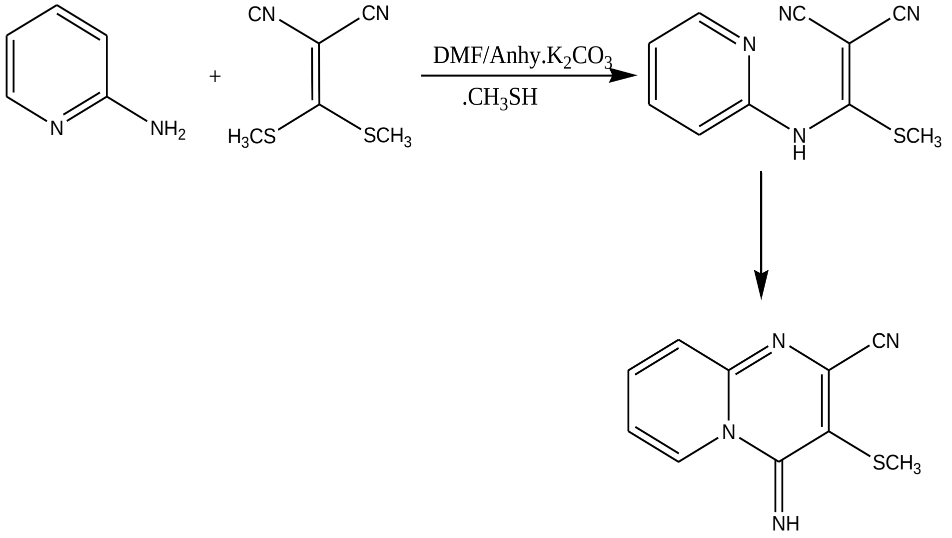


Reagents and conditions: (i) X, toluene, reflux.

34

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

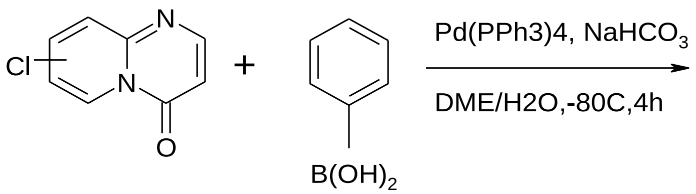
- The synthesis of 3-cyano-4-imino-2-methylthio-4H-pyrido[1,2-a] pyrimidine derivatives**(35)** were reported by **Vartale et al ., (2012)** by the reaction of bis (methylthio) methylene malononitrile and 2-amino pyridine in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate. The compounds have been screened as potent antioxidant agents. The results showed that the compound having a p-chloro aniline group on the iminopyrido[1,2-a]pyrimidine moiety as better antioxidant agent.

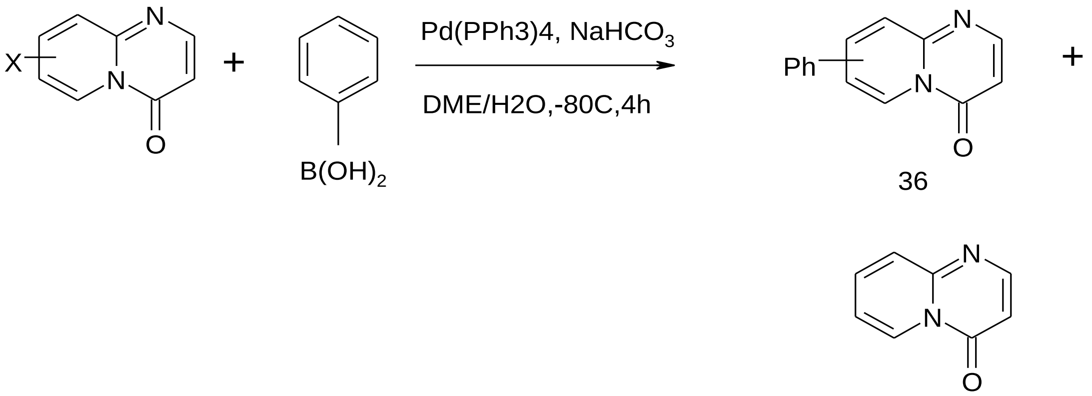


35

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

- The palladium-catalyzed Suzuki–Miyaura cross-coupling reactions were carried by **Molnar et al., (2011)** for the synthesis of aryl**(36)** and vinyl**(37)** 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.





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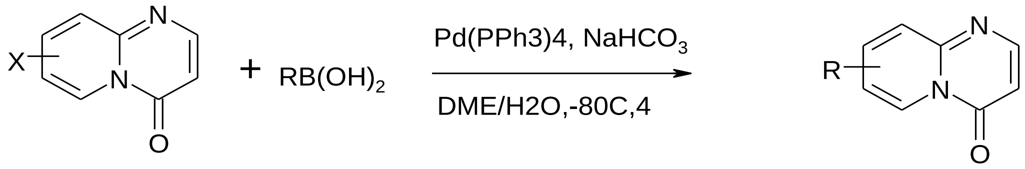
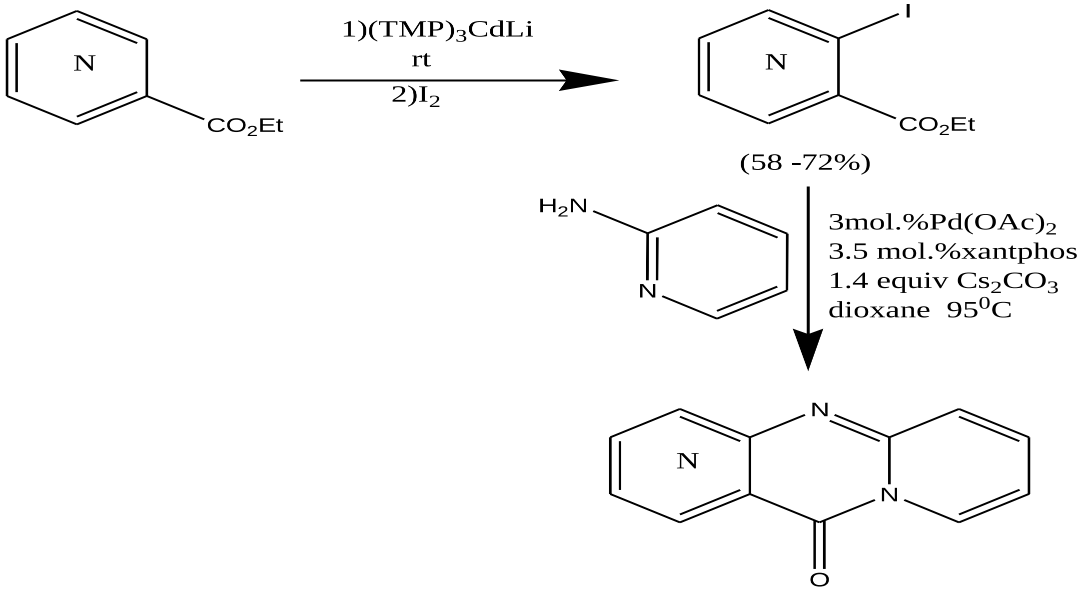


37

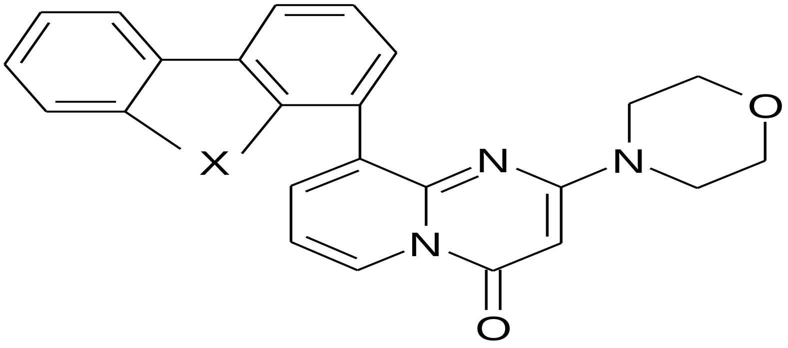
- ❖ Pyridine nitriles and esters were directly metalated using $(TMP)_3CdLi$ in tetrahydrofuran at room temperature by **Ababsa et al., (2010).** The 2-, 3-, and 4-cyanopyridines were treated with base for two hours, trapped with iodine to form iodo derivatives with the yield of 32 to 61%. Similarly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



38

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**(38)** 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**(39,40)** and 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.



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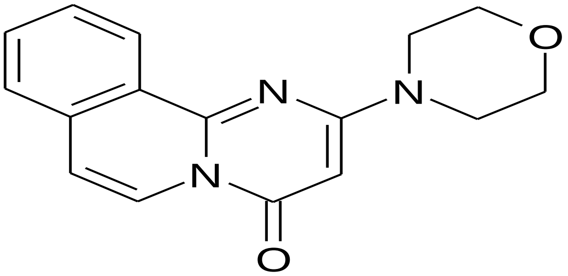
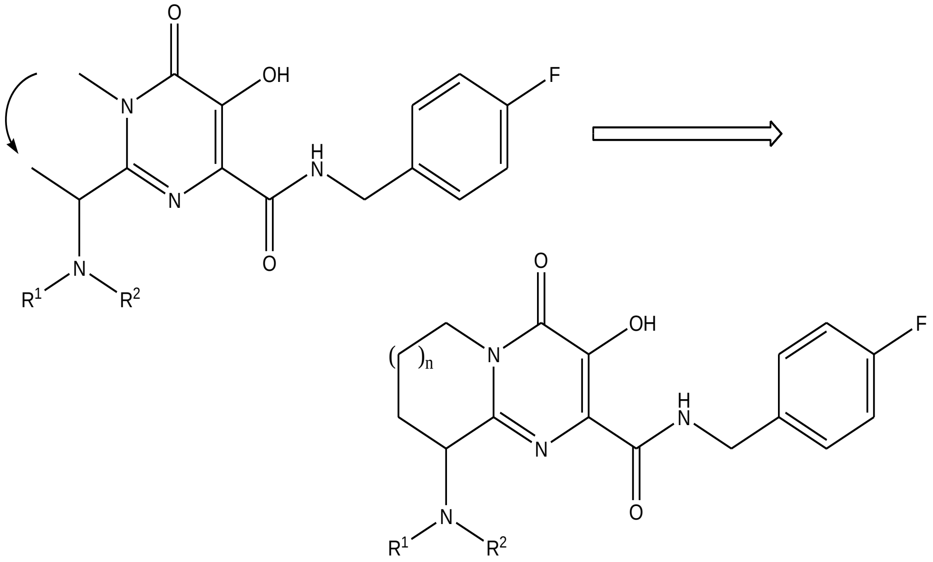


40

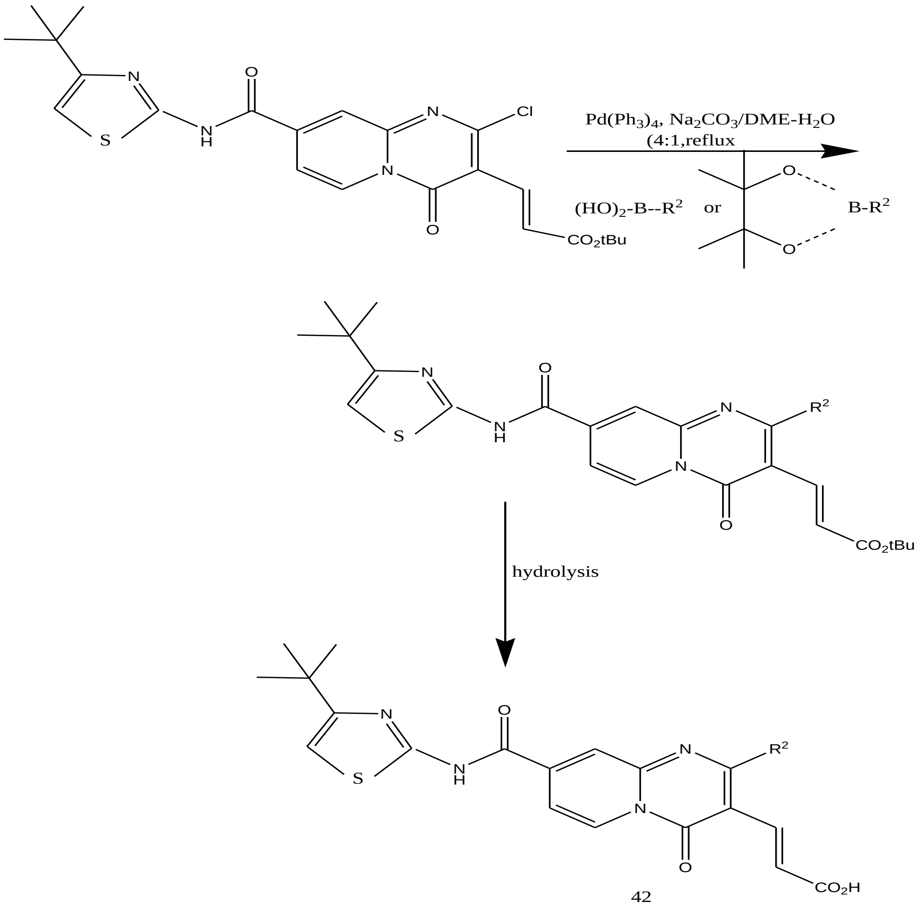
- Amine, amide, sulfonamide, sulfamide, and ketoamide derivatives of bicyclic pyrimidinones**(41)** were evaluated for HIV integrates inhibitors. Introducing a suitable substituted amino moiety modulated the physical-chemical properties of the molecules and conferred nanomolar activity in the inhibition 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).**



41

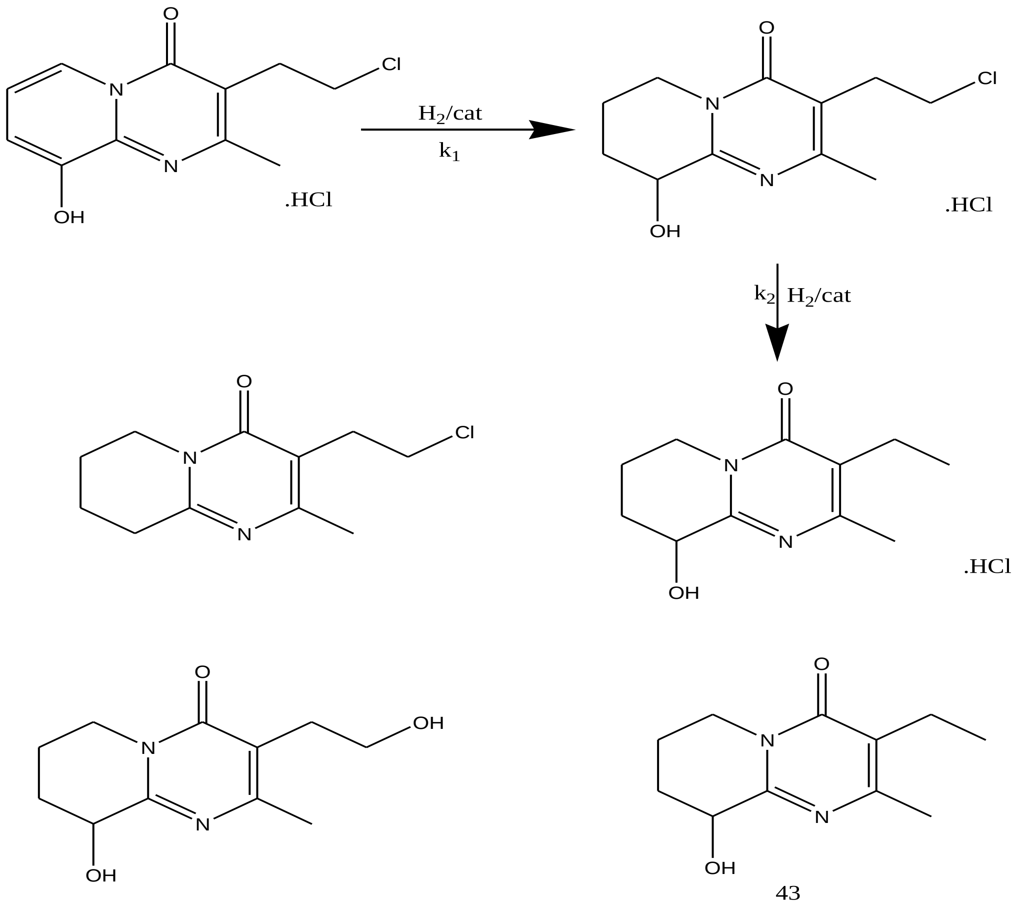
6a: n=0
6b: n=1
6c: n=2

- **Yoshida et al., (2006)** synthesized a series of 4-oxo-4H-pyrido[1,2-a]pyrimidine derivatives**(42)**, 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 substituents 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.



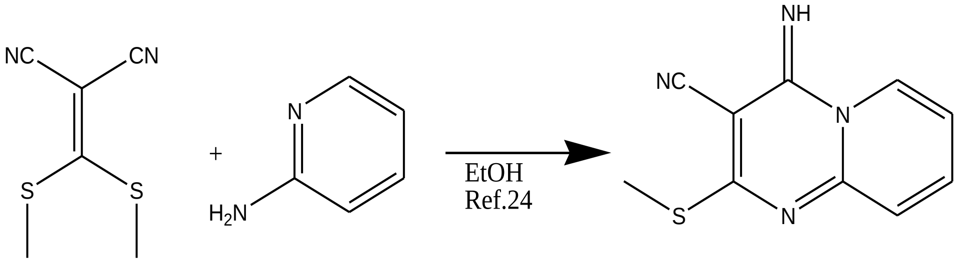
42

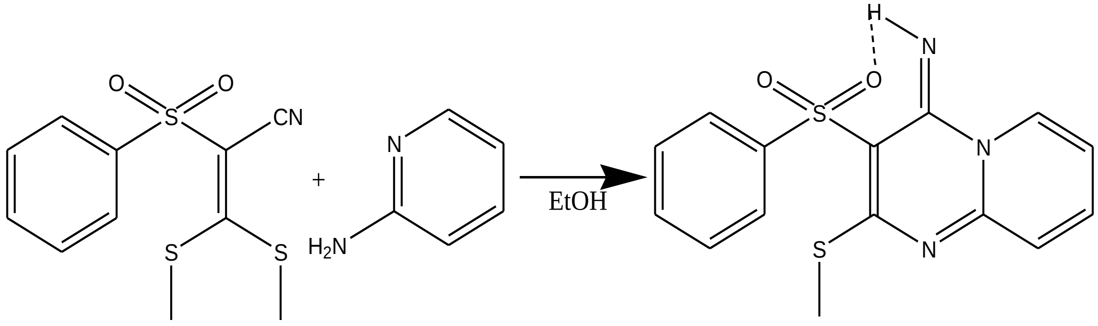
- Analytical technologies were used by **Smet et al ., (2005)** to solve the problem of selectivity in the hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride to 3-(2-chloroethyl)-6,7,8,9tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-onemonohydrochloride**(43)**. 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 easierimplementation. 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 adjustand confirm this method.



43

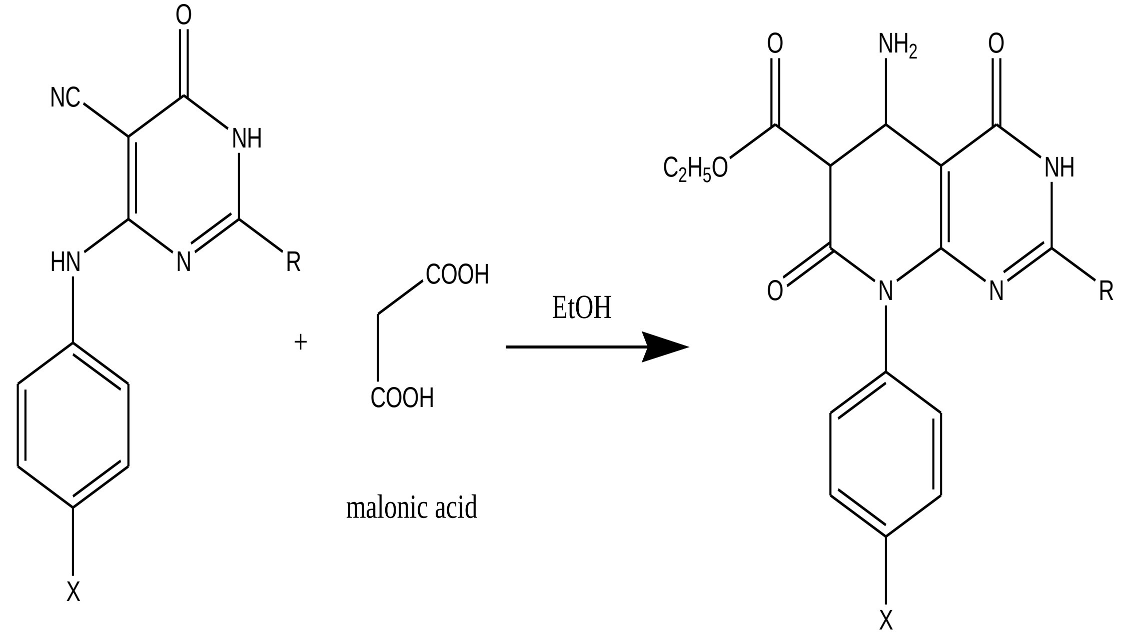
- (*E*)-3-(Benzenesulfonyl)-2-(methylsulfanyl)pyrido-[1,2-*a*]pyrimidin-4-ylidenamine**(44)** was identified by **Yong et al.,(2003)** as a potent and selective 5-HT6 antagonist, and a one-step synthesis has been developed for the same. This compound represents a distinct novel chemo type of 5-HT6 ligands and was expected to be a useful tool for further pharmacological evaluation of the function of the 5-HT6 receptors.





44

- Some novel Pyridopyrimidine carboxylate**(45)** 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 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 Aspergillusniger*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).**



45

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

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

The Infrared (IR) spectra were recorded in KBr pellet technique on a **IR-AFFINITY-I.** Absorption frequencies were quoted in reciprocal centimeter.

Nuclear Magnetic Resonance (^{1}H-NMR) spectra were determined by BrukerAvance 400MHz NMR instrument in d-DMSO,$CDCL_3$ and D_2O as solvents, with tetra methyl silane as the internal reference. Chemical shift were quoted in parts per million (ppm).

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 iodine.

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

3.2 Preparation of Amide

3.2.1. Preparation of 5-(3-methylpyridin-2-ylamino)-5-oxo pentanoic acid (48a)

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(48b)

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 of5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid(48c)

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 5-(3-methylpyridin-2-ylamino)-5-oxo pentanoic acid (49a)

2.5mM of 5-(3-methylpyridin-2-ylamino)-5-oxo pentanoic acid **(49a)**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 recrystallized with acetone to get pure white crystals.

3.3.2. Preparation of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid(49b)

2.5mM of5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid**(49b)**was taken in the 25ml round bottomed flask. To this added 5omg 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 recrystallized with acetone to get pure white crystals.

3.3.3. Preparation of5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid(49c)

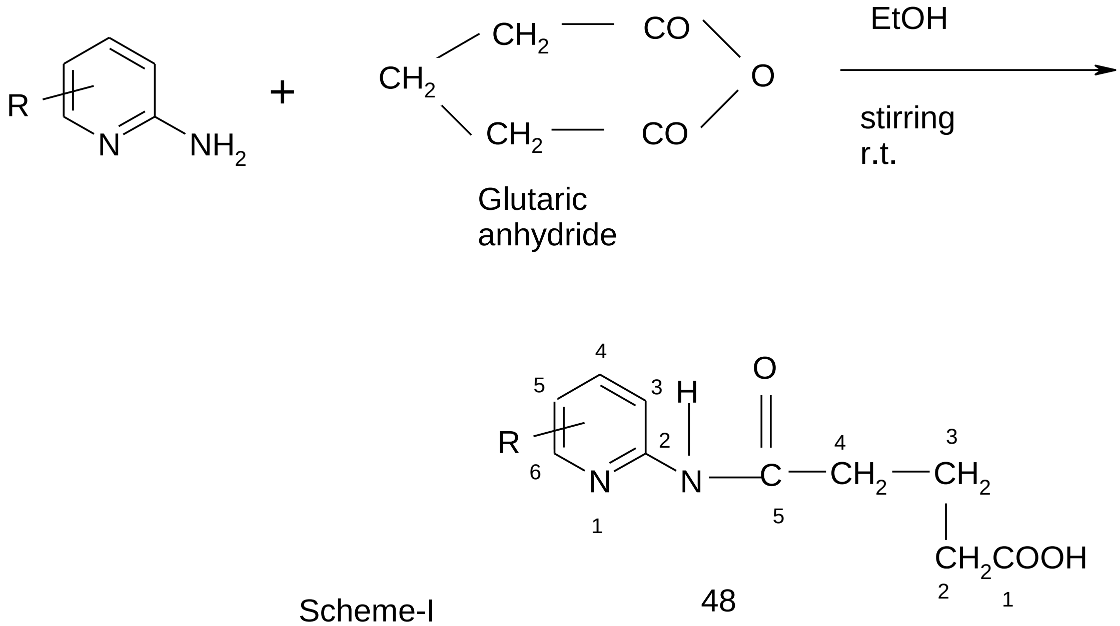
2.5mM of5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid**(49c)**wastaken in the 25ml round bottomed flask. To this added 50mg of PTSAs. Then 10ml of alcohol was added and the mixture was kept for reflux in a water bath for 4 hours. The reaction was monitored by TLC. After the completion of the reaction 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 recrystallized with acetone to get pure white crystals.

RESULT S AND DISCUSSION

4. RESULTS AND DISCUSSION

4.1. Preparation of pyridine-2-ylamino-5-oxopentanoic acid (48)

The reaction of 2- amino pyridine with succinic anhydride has been reported by **Kolotova et al., (2001).**Following the same procedure, we carried out the reaction of 2-aminopyridine with Glutaric anhydride.



Scheme-I

48

R	Compound
3Me	48a
6Me	48b
5Br	48c

The compound (**48**,**Scheme-1**) was obtained by stirring alcoholic solution of 2-aminopyridine with glutaric anhydride. The TLC showed single spot, indicating the formation of only one product. The yield of the product was found to greater with the range of 90-94% after recrystallization with alcohol. The yields and the melting point of the compounds are given in table-I.

Table-I

Yield and Melting Point Values of the Compounds(48a-48c)

Compound	**Yield**	**Melting point**
48(a)	91%	251°
48(b)	94%	255°
48(c)	92%	272°

The structures of the compounds (48a-48c) were confirmed by IR and ^{1}H NMR studies.

5-(3-methylpyridin-2-ylamino)-5-oxo pentanoic acid (48a)

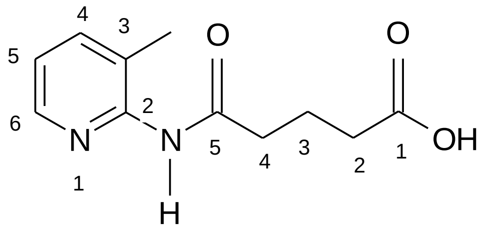


Figure VI1 gives the **IR** spectrum of 5-(3-methylpyridin-2-ylamino)-5-oxo pentanoic acid **(48a)**.

IR was recorded **IR-AFFINITY-I** using **KBr pellet technique**. The IR showed absorption at 3078-3039cm^{-1}, 1666cm^{-1} indicating the presence of –COOH group. The absorption at 3317.56cm^{-1} showed the presence of 'NH' group. The 'CO' absorption was observed at 1743cm^{-1}.

Figure Igives^{1}HNMR of the compound (**48a**). NMR was recorded using deuterated DMSO.

- Analysis of the ^{1}HNMR revealed totally presence of 13 protons in the compound.
- A singlet of δ 2.02 integrating for three proton was due to CH_3 group attached to 3rd position of the pyridine nucleus.
- A pentet at δ 1.67 –δ 1.74 integrating for two proton, and triplet integrating for four proton at δ 2.24 –δ 2.26 indicated the presence of $–CH_2 –CH_2 – CH_2 –$ moiety in the structure.
- In the aromatic region three protons were observed. The proton resonating at, more downfield (i.e) at δ7.6 - 7.7 was assigned to H_6, since it is nearer to ring nitrogen, it is de shielded.
- Also the proton resonating at δ 7.2 – 7.3 as multiplet was assigned to H_4. Since it experiences deshielding effect due to the $–CH_3$- group on the 3rd position.
- H_5 comes under the shielded region of the pyridine ring, hence an up field shift was observed. H_5 resonates at δ6.44 - δ6.47 as quartet.
- At δ 5.67, a broad hump was observed, integrating for one proton. This was attributed to the –NH- group in the compound.

Hence the proposed structure was confirmed for compound (**48a**).

Also similar peaks were observed with a little shift in the δ values for the compounds **48b&48c**. In the case of compound (**48b**) NH peak was not observable. Since the spectrum was recorded in the D_2O solvent. Commercial D_2O may containsome amount of H_2Oas a impurity & hence exchange of 'NH' peak with proton of solvent would have occurred. For the compound (**48c**) both NH peak (δ 6.2) as well as carbonyl proton at δ12.1 was observed, because the solvent used for recording this compound was $CDCl_3$.

The **NMR** data of the compound (**48b&48c**) along with positions are tabulated in table II & III.

5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid(48b)

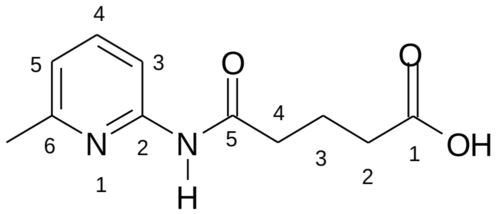


Table II

^{1}H NMR Values of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid (48b)

δ in ppm	**Number of ^{1}H**	**Assignment**
1.71-1.19	2	H_3 of acid
2.3	3	Methyl proton of C_6
2.21-2.37	4	H_2 & H_4 of acid moiety
6.62-6.4	1	H_5 of ring
6.709-6.731	1	H_4 of ring
7.6-7.72	1	H_3 of ring

5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid(48c)

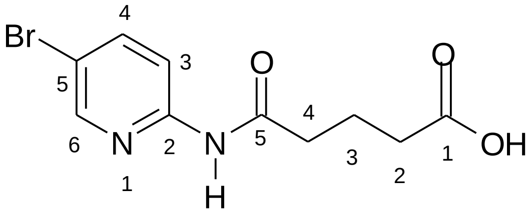


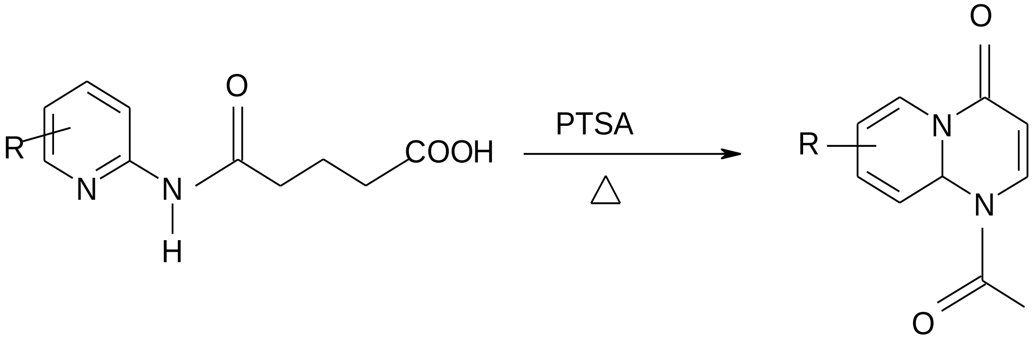
Table-III

^{1}H NMR Values of 5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid(48c)

δ in ppm	Number of ^{1}H	Assignment
1.66-1.74	2	H_3 of acid moiety
2.22-2.26	4	H_2 of acid moiety
7.4-7.5	1	H_3
7.93-7.94	2	H_4 and H_6
6.12	2	(N-H)
12.1	1.12	H1(COOH)

4.2. Cyclisation of (3-methyl pyridine-2- ylamino)-5-oxo pentaholic acid (49)

For the Cyclisation of (3-methyl pyridine-2- ylamino)-5-oxo pentaholic acid PTSA was catalyst used as cyclizing agent **(Scheme-II).** The reaction was carried out under reflux in a steam bath, for 3-4hrs. Progress of the reaction was monitored by TLC. TLC showed one major and minor peaks indicating the formation of byproducts. Hence the yields of the compounds were on the range of 50-60%, after recrystallization.



Scheme-II 49

R	Compound
9Me	49a
6Me	49b
7Br	49c

Formation of the 1-acteyl pyrido[1,2-a]pyridine-4-(9aH)-ones were confirmed by IR and ^{1}HNMR spectral studies.

1-acetyl-3-methyl-^{1}H pyrido[1,2-a] pyrimidin-4-(9aH)-ones (49a)

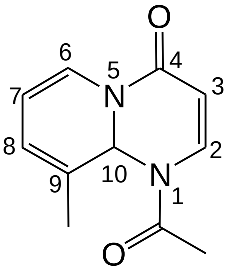


Figure IX gives the IR spectrum of compound (**49a**)

The IR showed the characteristic absorption of ‘CO’ at 1674.24 cm^{-1}& 1612cm^{-1}

The NMR spectrum of compound (**49a**) displayed six sets of signals, accounting for eleven protons. **Figure IV**gives NMR of compound (**49a**).

- A singlet integrating for three protons, at δ 2.28, accounts for the methyl group in the pyrido ring of the compound.
- Another signal at δ 2.15 integrating for three protons was observed, which indicated the presence of one more 'methyl' group, in the system, other than that from the starting compound. This was attributed to the acetyl group attached to the nitrogen.
- In the aromatic region, four signals accounting for six protons were observed. The overlapping signals at δ 7.69-7.74 for two protons was assigned to H_2 .Since it experiences more deshielding effect of nitrogen as well as acetyl group and H_6 ,since it also comes under the anisotropy effect of C=O at the 4th position.**(Al Jallo and Al Biaty,1978)**
- A doublet of doublet at δ 7.43-7.49 integrating for one proton was attributed to H_1
- A doublet at δ 7.1-7.12 integrating for two proton was assigned to H_8 and H_3 protons.
- A triplet at δ 6.544-6.577 integrating for one proton was assigned to $H_{7.}$ Thus the structure was confirmed.

The **NMR** data of the compound (**49b&49c**) along with positions are tabulated in table IV&V.

1-acetyl-6-methyl-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one(49b)

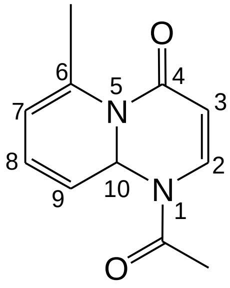


Table IV

^{1}H NMR Values of 1-acetyl-6-methyl-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one(49b)

Δ	**Number of ^{1}H**	**Assignment**
2.29	3	CH_3 of C_6
2.35	3	CH_3 of C_{12}
6.321-6.339	1	H_7
6.81-6.833	1	H_3
7.117-7.137	1	H_{10}
7.434-7.456	1	H_8
7.474-7.777	1	H_2

1-acetyl-7-bromo-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one(49c)

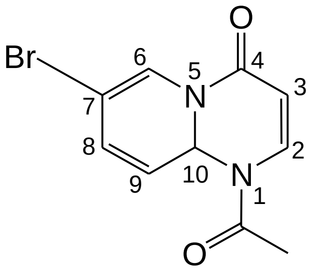


Table V

^{1}H NMR Values of 1-acetyl-7-bromo-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one(49c)

δ	**Number of ^{1}H**	**Assignment**
2.29	3	CH_3 of C_{12}
6..9-6.92	1	H_3 and H_9
7.12-7.14	2	H_8
7.506-7.526	2	H_{10}
7.9-8.0	1d	H_6
8.19-8..2	1	H_2

Figure – I: ^{1}H NMR of 5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid(48a)

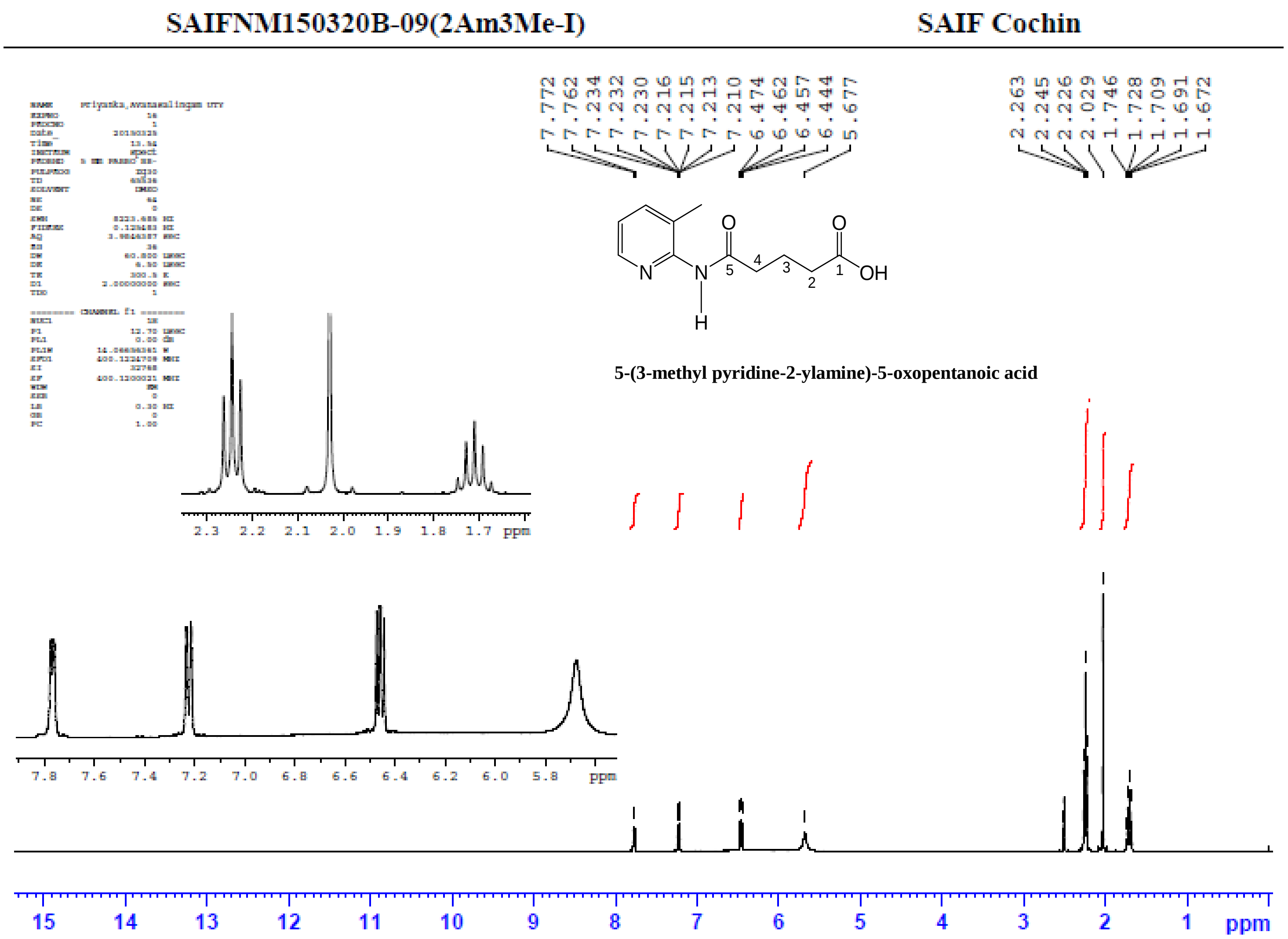


Figure -II: ^1H NMR of 5-(6-methylpyridine-2-ylamine)-5-oxopentanoic acid(48b)

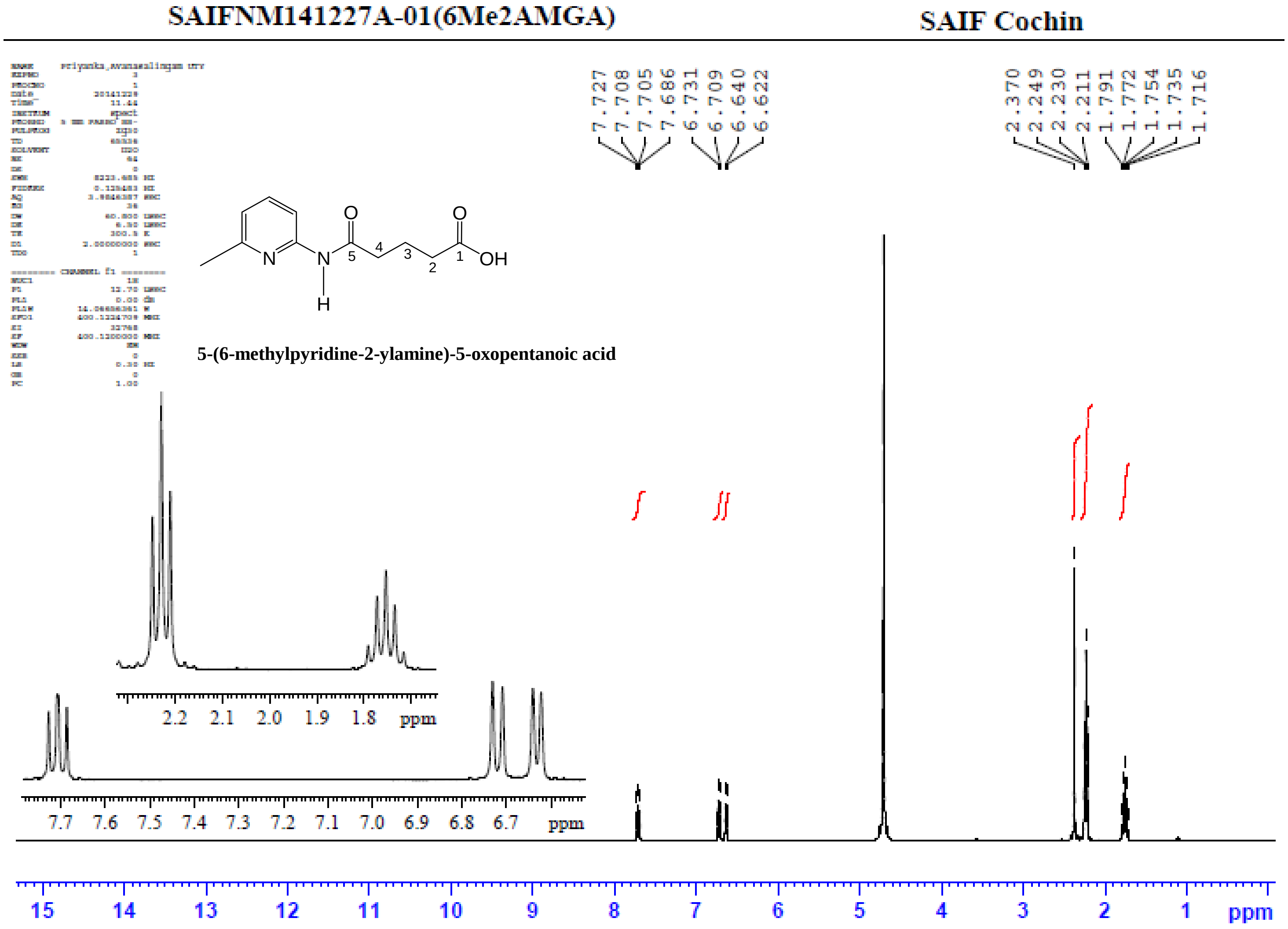


Figure - III: ^{1}H NMR of 5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid(48c)

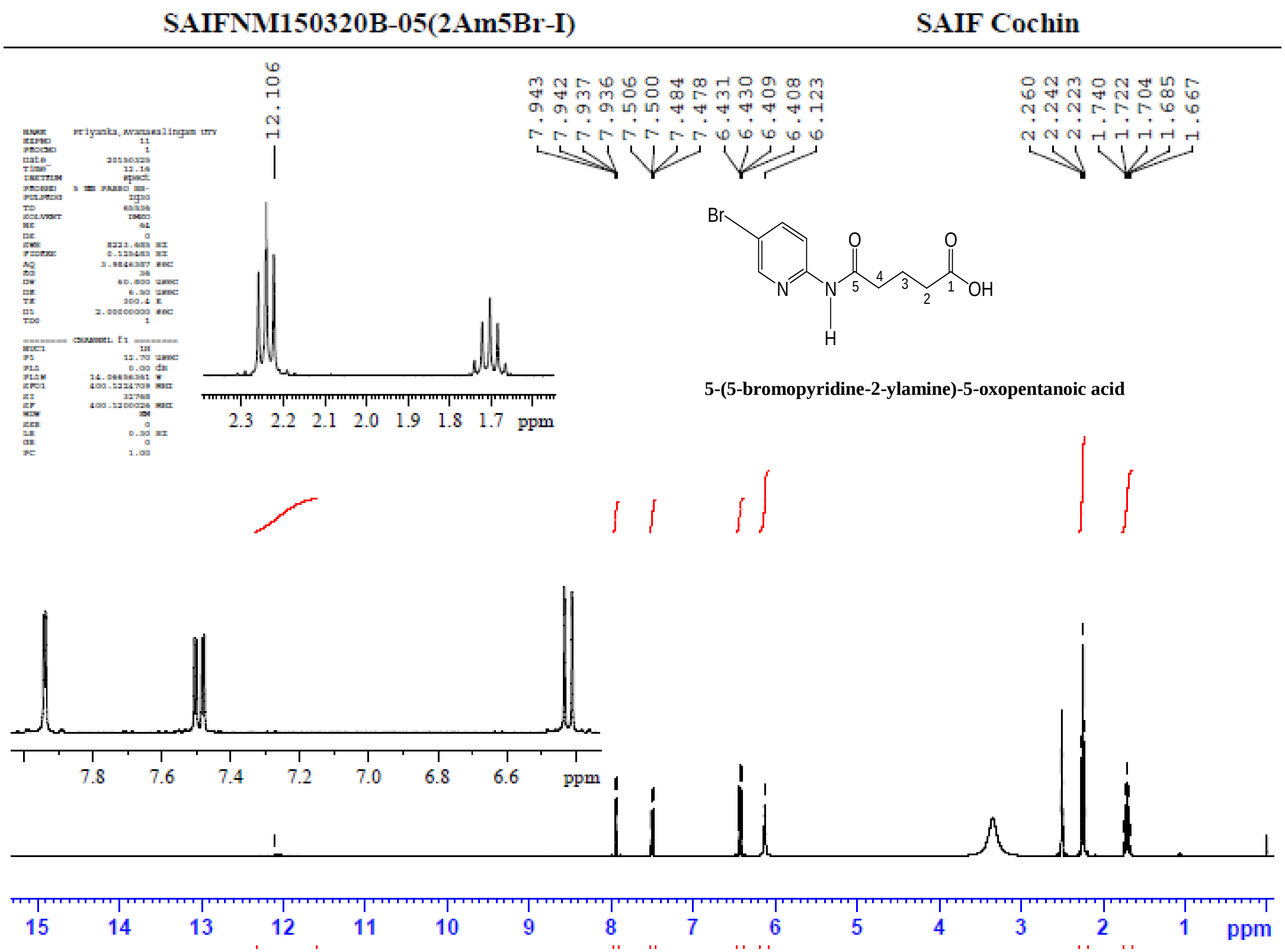


Figure - IV:^{1}H NMR of 1-acetyl-9-methyl-1H-pyrido [1, 2-a] pyrimidin-4(9aH)-one(49a)

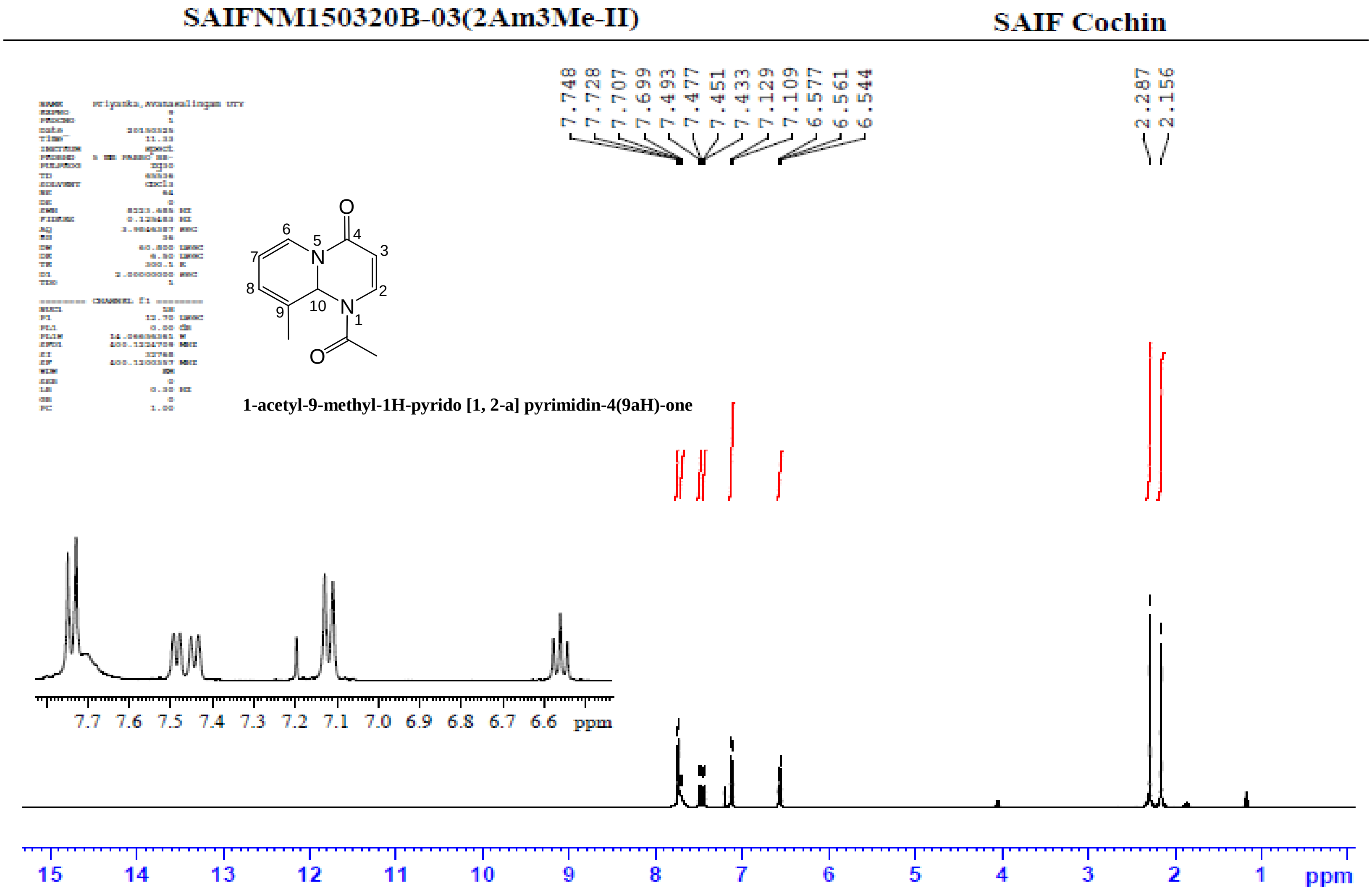


Figure – V: ^{1}H NMR of 1-acetyl-6-methyl-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one(49b)

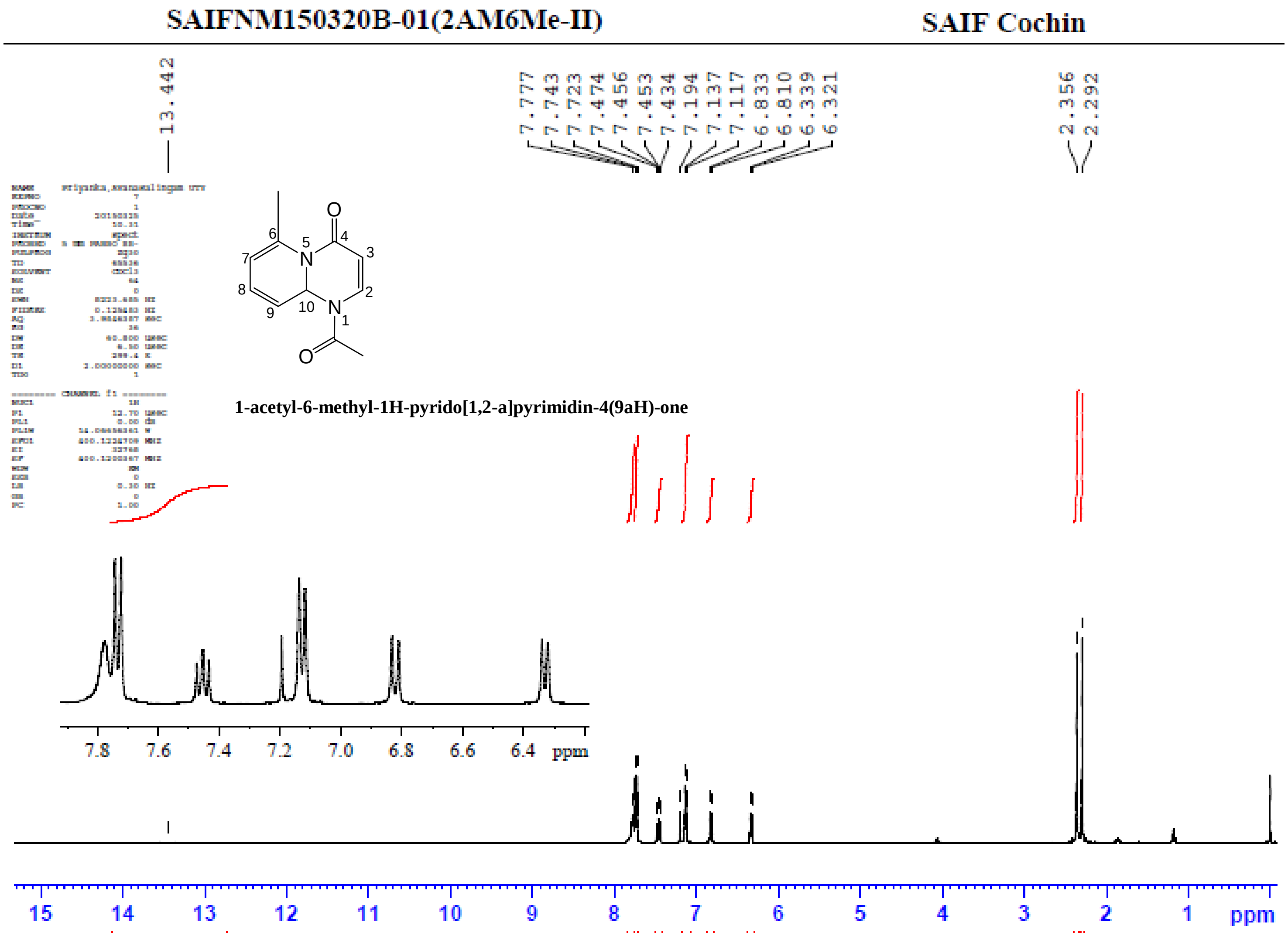


Figure – VI: ^{1}H NMR of 1-acetyl-7-bromo-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one(49c)

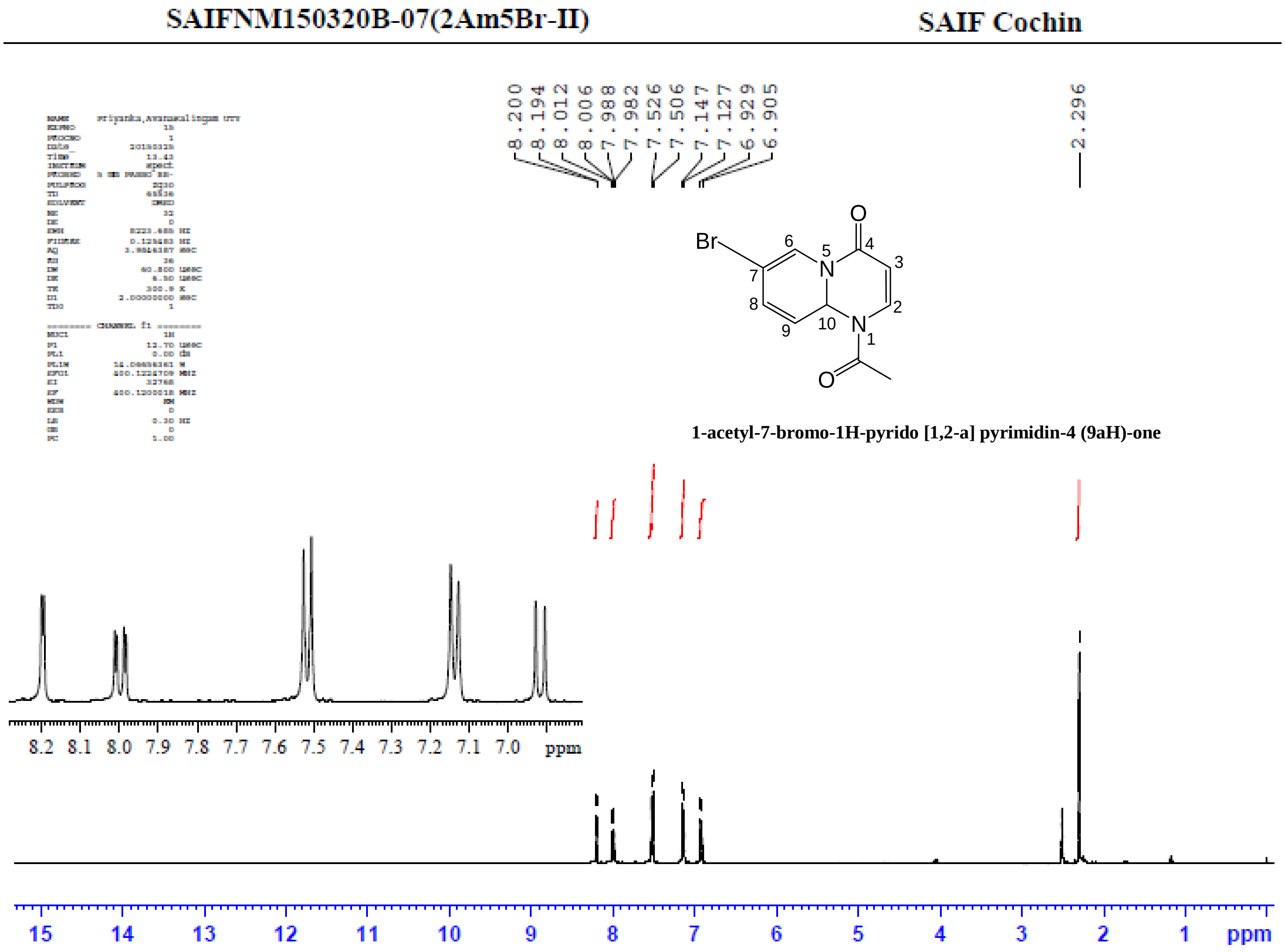


Figure – VII: IR spectrum of 5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid(48a)

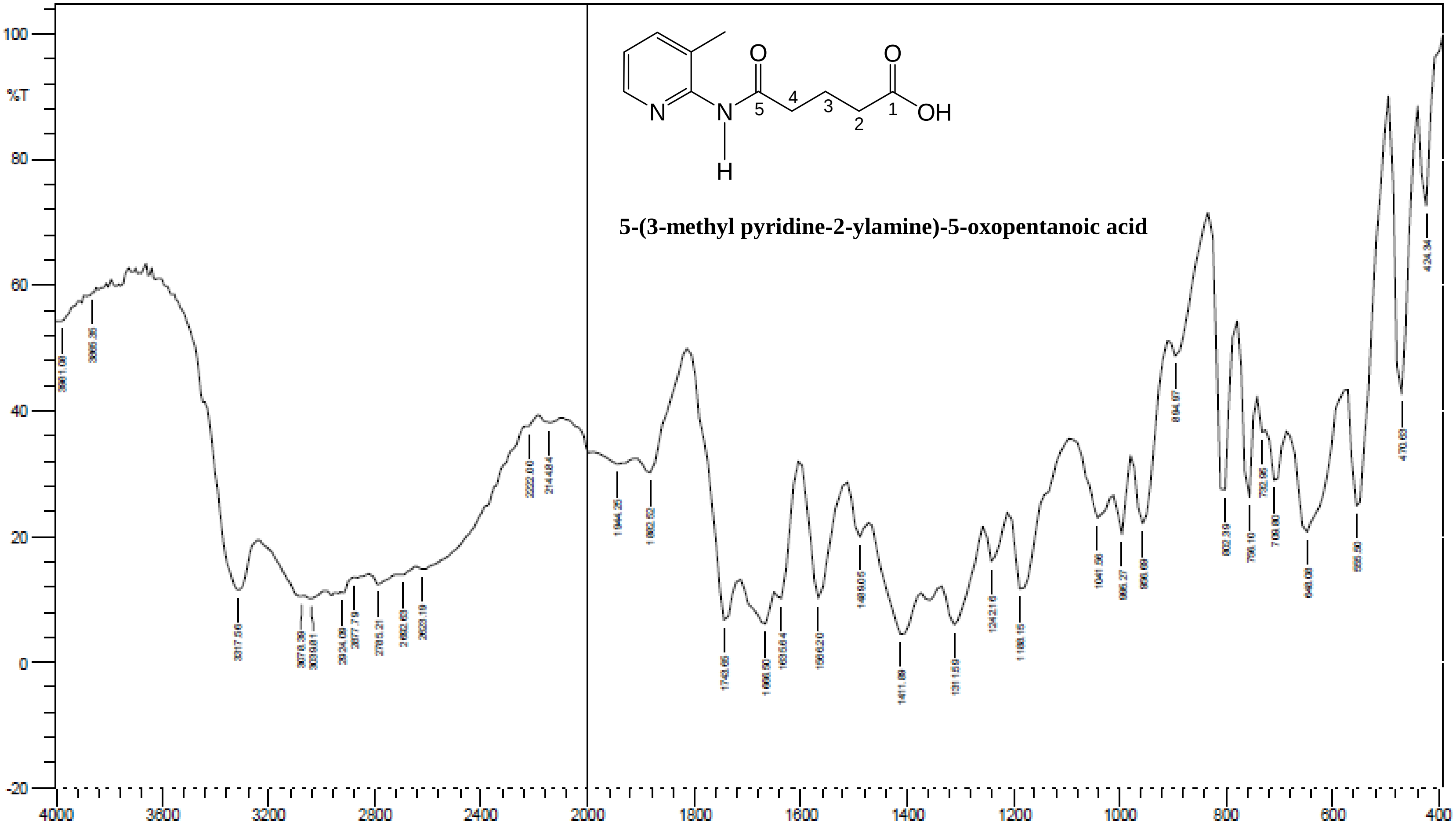

5-(3-methyl pyridine-2-ylamine)-5-oxopentanoic acid

Figure - VIII: IR spectrumof 5-(5-bromopyridine-2-ylamino)-5-oxopentanoic acid(48c)

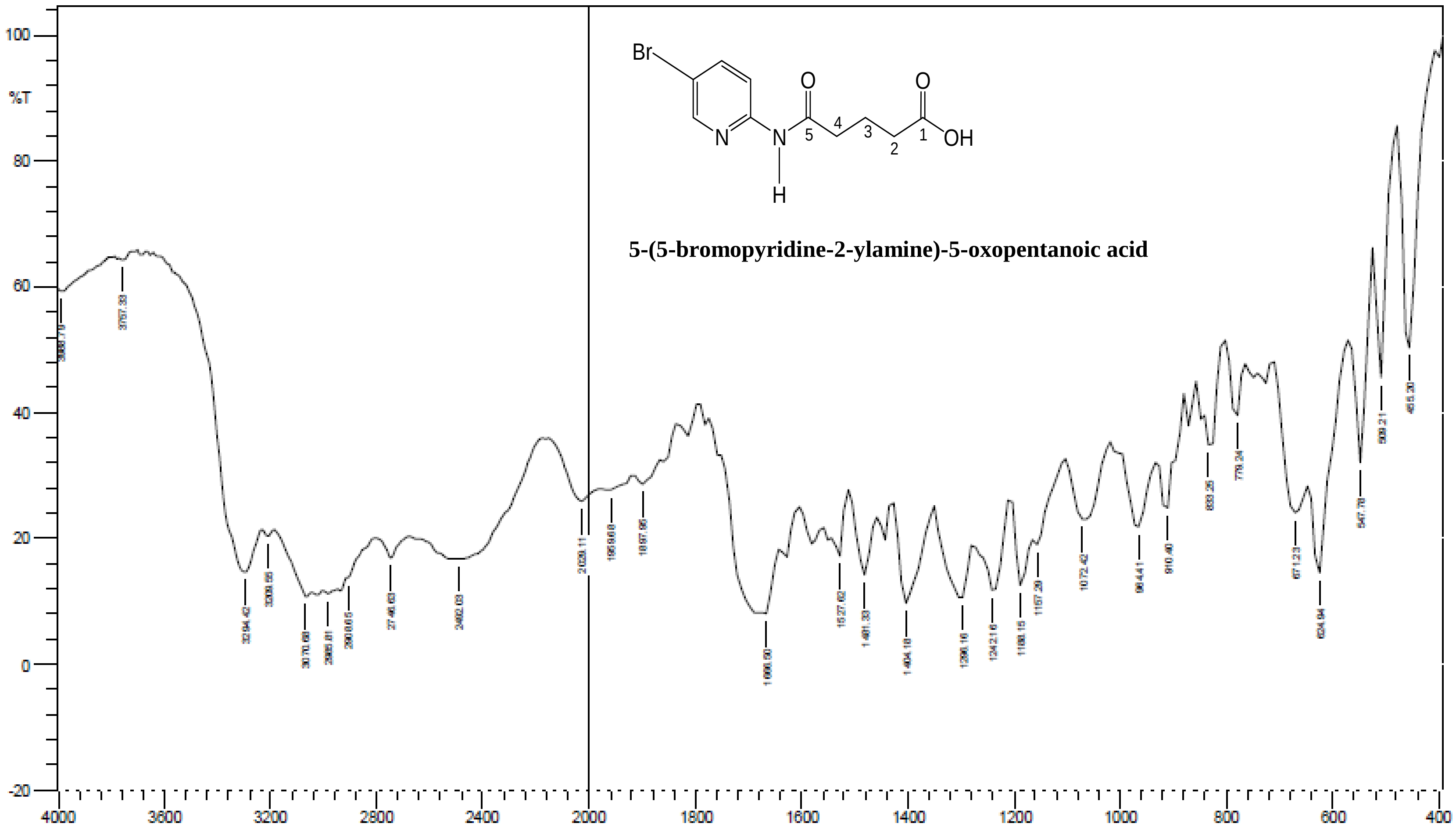


Figure - IX: IR spectrum of 1-acetyl-9-methyl-1H-pyrido [1, 2-a] pyrimidin-4(9aH)-one 49(a)

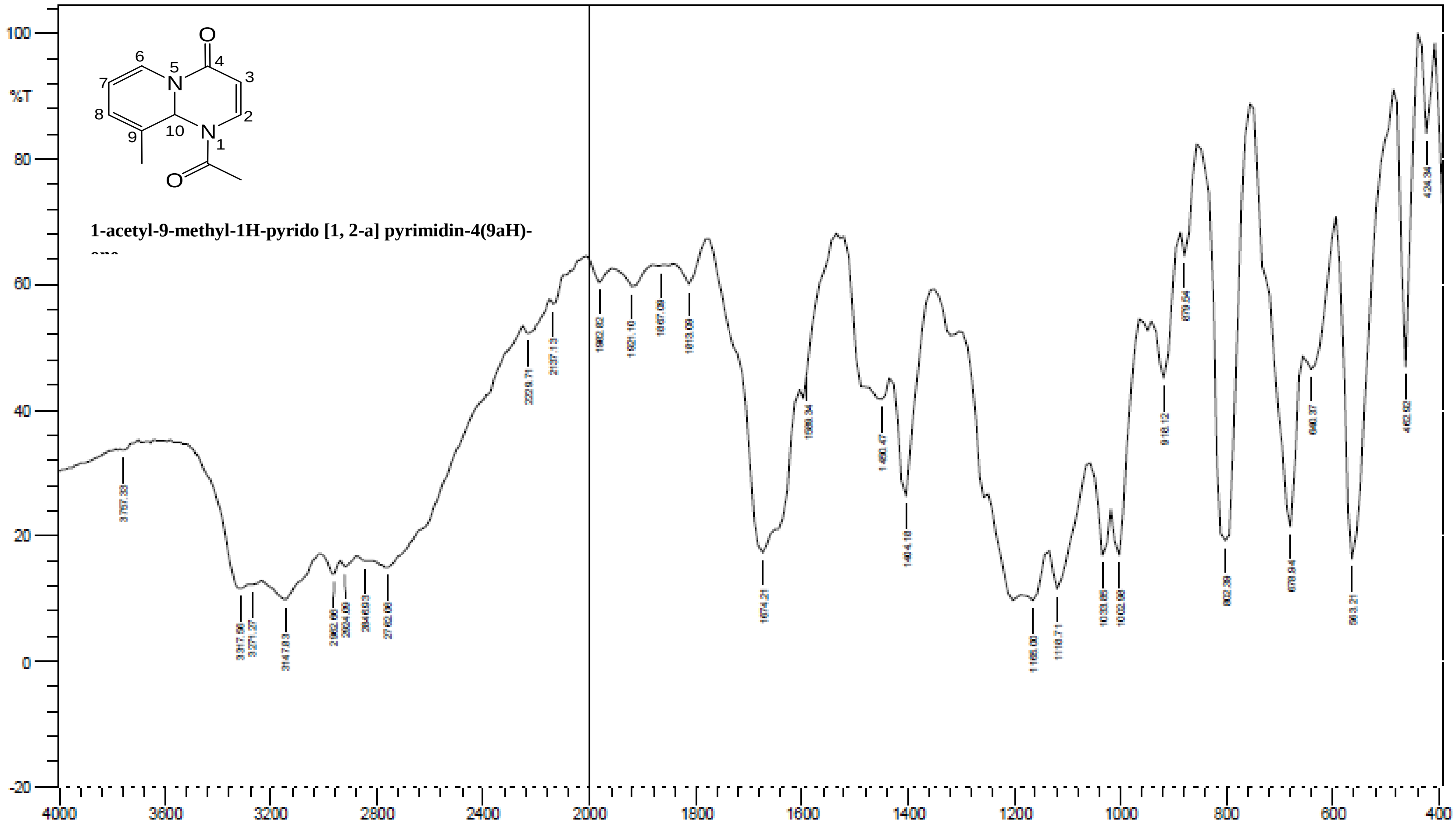
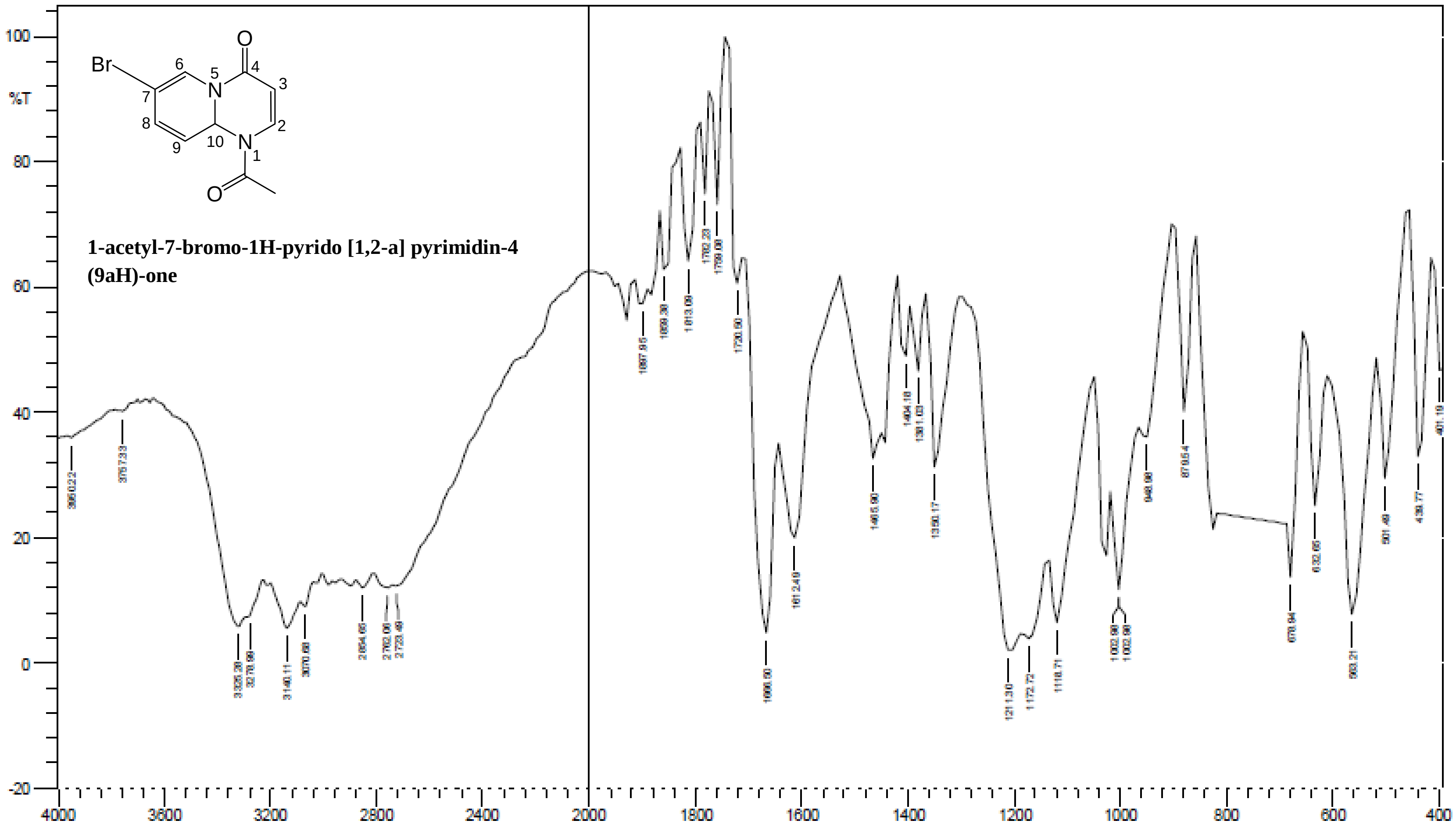


Figure – X: IR spectrum of 1-acetyl-7-bromo-1H-pyrido[1,2-a]pyrimidin-4(9aH)-one (49c)



SUMMARY AND CONCLUSION

5. SUMMARY AND CONCLUSION

The results of the reaction of 2-amino pyridine with glutaric anhydride are summarized below

- The reaction of 2-amino pyridine with glutaric anhydride yielded the amide viz 5-(pyridin-2-ylamino)-5-oxopentanoic acid in excellent yields at room temperature.

- The cyclisation of the amide was carried out using PTSA as catalyst under reflux in a steam bath to yield 1-acetyl-1H-pyrido[1,2-a]pyrmidin-4(9aH)-one. The yield of the compounds was moderate.

- The synthesized compounds were characterized by IR and 1HNMR spectral studies.

- The IR and ^{1}H NMR data showed good correlation with the proposed structure.

- Thus an environmentally benign synthesis of pyrido[1,2-a]pyrimidin-4-ones is developed.

- The method is simple and cost effective and does not require strong hazardous acids like PPA and high temperature.

- Hence this successful cyclization reaction may find important a application in the synthesis of pyrimidine derivatives.

REFERENCES

REFERENCES

- AbabsaGheniaBentabed, SidatyCheikh Sid Ely, Stephanie Hesse, EkhlassNassar, FlorisChevallier, Tan Tai Nguyen, Aı¨chaDerdour and Florence Mongin(2010), “Direct Metalation of Heteroaromatic Esters and Nitriles Using a Mixed Lithium-Cadmium Base. Subsequent Conversion to Dipyridopyrimidinones”, *J. Org. Chem* 75, 839-847.
- Abass Mohamed, Mostafa M. Ismail, Wafaa R. Abdel-Monem, Aisha S. Mayas, (2009), “Substituted pyridopyrimidinones. Part 5. Behaviorof 2-hydroxy-4-oxo-4-pyrido[1,2-_]pyrimidine-3-carbaldehydein nucleophilic condensation reactions”, *Chemical Papers*, 64 (1), 72–83.
- AbhaBishnoia, SuruchiSingha, Anil K Tiwaria, Krishna Srivastavab, Ram Raghuvirc And Chandrakant M Tripathi, (2013), “Synthesis, Characterization And Biological Activity Of New Cyclization Products Of 3-(4-Substituted Benzylidene)-2*h*-Pyrido[1,2-*A*]Pyrimidine 2,4-(3*h*)-Diones”, *J. Chem. Sci.* Vol. 125, No. 2, Pp. 305–312
- Annam´ariaMoln´ar, Anita Kapros,L´aszl´oP´ark´anyi,Zolt´anMucsi,G´aborVl´adand Istv´anHermecz, (2011), “Suzuki–Miyaura cross-coupling reactions of halo derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones”,*Organic &Biomolecular Chemistry*, 9, 6559
- BarlaamBernard, Sabina Cosulich, SébastienDegorce, Martina Fitzek,FabrizioGiordanetto, Stephen Green, TordInghardt, Laurent Hennequin,UrsHancox, Christine Lambert-van der Brempt, RémyMorgentin, Sarah Pass,Patrick Plé, TwanaSaleh, Lara Ward, (2014), “Discovery of 9-(1-anilinoethyl)-2-morpholino-4-oxo-pyrido[1, 2-a]pyrimidine-7-carboxamides as PI3Kb/d inhibitors for the treatment of PTEN-deficient tumours”, *Bioorganic & Medicinal Chemistry Letters*, 24, 3928–3935
- BishnoiaAbha, SuruchiSingha, Anil K Tiwaria, Krishna Srivastavab, Ram Raghuvirc And Chandrakant M Tripathi, (2013), “Synthesis, Characterization And Biological Activity Of New Cyclization Products Of 3-(4-Substituted

Benzylidene)-2h-Pyrido[1,2-A]Pyrimidine 2,4-(3h)-Diones",*J. Chem. Sci.*Vol. 125, No. 2, Pp. 305–312.

- BuillaJulio Alvarez, and BarluengaJos_e, (2011), "Heterocyclic Compounds: An Introduction", *Modern Heterocyclic Chemistry,* First Edition, Published by Wiley-VCH Verlag GmbH & Co. KGaA.
- Cano Eline, Olivier R. Barbeau, Christine Bailey, Xiao-Ling Cockcroft, Nicola J. Curtin, Heather Duggan, Mark Frigerio, Bernard T. Golding, Ian R. Hardcastle, Marc G. Hummersone, Charlotte Knights, Keith A. Menear, David R. Newell, Caroline J. Richardson, Graeme C. M. Smith, Ben Spittle and Roger J. Griffin, (2010), "DNA-Dependent Protein Kinase (DNA-PK) Inhibitors. Synthesis and Biological Activity of Quinolin-4-one and Pyridopyrimidin-4-one Surrogates for the Chromen-4-one Chemotype", *J. Med. Chem*., 53, 8498–8507.
- ChSanjeeva Reddy and M Raghu, (2008), "p-toluenesulfonic acid catalyzed rapid and efficient protocol for one-pot synthesis of a-amino nitriles", *Indian journal of chemistry*, vol. 47B, pp. 1572-1577.
- Eline Cano, Olivier R. Barbeau, Christine Bailey, Xiao-Ling Cockcroft, Nicola J. Curtin, Heather Duggan,Mark Frigerio, Bernard T. Golding, Ian R. Hardcastle, Marc G. Hummersone, Charlotte Knights, Keith A. Menear,David R. Newell, Caroline J. Richardson, Graeme C. M. Smith, Ben Spittle and Roger J. Griffin, (2010),"DNA-Dependent Protein Kinase (DNA-PK) Inhibitors. Synthesis and Biological Activityof Quinolin-4-one and Pyridopyrimidin-4-one Surrogates for the Chromen-4-one Chemotype",*J. Med. Chem*., 53, 8498–8507
- Girreser Ulrich, UllviBluhm, Bernd Clement and Dieter Heber (2013), "^{1}H, ^{13}C and ^{15}N NMR spectral analysis of substituted 1,2,3,4-tetrahydro-pyrido[1,2-a]pyrimidines",*Magn. Reson. Chem* 51, 714-721.
- GrummtUlrich-W., Dieter Weiss, EckhardBirckner, and R. Beckert, (2007), "Pyridylthiazoles: Highly Luminescent Heterocyclic Compounds", *J. Phys. Chem. A*, *111*, 1104-1110.
- GuoChuangxing, Angelica Linton, MehranJalaie, Susan Kephart, Martha Ornelas, Mason Pairish, Samantha Greasley, Paul Richardson, Karen Maegley, Michael Hickey, John Li, Xin Wu, XiaodongJi, ZhiXie, (2013), "Discovery of 2-

((1H-benzo[d]imidazol-1-yl)methyl)-4H-pyrido [1,2-a]pyrimidin-4-ones as novel PKM2 activators”,*Bioorganic & Medicinal Chemistry Letters*, 23, 3358–3363

- GuoChuangxing, Angelica Linton, MehranJalaie, Susan Kephart, Martha Ornelas, Mason Pairish, Samantha Greasley, Paul Richardson, Karen Maegley, Michael Hickey, John Li, Xin Wu, XiaodongJi, ZhiXie, (2013), “Discovery of 2-((1H-benzo[d]imidazol-1-yl)methyl)-4H-pyrido [1,2-a]pyrimidin-4-ones as novel PKM2 activators”,*Bioorganic & Medicinal Chemistry Letters*, 23, 3358–3363
- Hajimahdi Z., Zarghi, A., Zabihollahi, R.,Aghasadeghi, M. R. (2013), “Synthesis, biological evaluation, and molecular modeling studies of new 1,3,4-oxadiazole- and 1, 3, 4-thiadiazole-substituted 4-oxo-4H-pyrido[1,2-a]pyrimidines as anti-HIV-1 agents”,*Med Chem Res* 22, 2467-2475.
- HizaddinHanee F., Mohd. Ali Hashim, and RamalingamAnantharaj, (2013), “Evaluation of Molecular Interaction in Binary Mixture of Ionic Liquids Heterocyclic Nitrogen Compounds: Ab Initio Method and COSMORS Model”, *Ind. Eng. Chem. Res.*, 52, 18043−18058.
- Huaihong Zhang, Rong Huang, ZhaoshengCai, ChunxiangXu, Baiwang Sun, (2013),”2-Methyl-3-chloro-9-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidineHydrochloride: Crystal Structure and Interaction with DNA”,*J ChemCrystallogr*, 43:70–75
- Kai Yang, Jinbao Xiang, GuochenBao, Qun Dang, and XuBai, (2013), “Synthesis of Highly Substituted 4H-Pyrido[1,2-a]pyrimidines via a One-Pot Three-Component Condensation Reaction”, *ACS Comb. Sci.*, 15, 519−524
- Mane Uttam R., D. MohanakrishnanDinkarSahal, Prashant R. Murumkar, RajaniGiridhar and Mange Ram Yadav, (2014), “Synthesis and biological evaluation of some novel pyrido[1,2-a]pyrimidin-4-ones as antimalarial agents”, *European Journal of Medicinal Chemistry*, 79, 422 - 435
- Mane, U. R., Li, H., Huang, J., Gupta,R. C., Nadkarni, S. S., Giridhar, R., Naik, P. P., Yadav, M. R. (2012), “Pyrido[1,2-a]pyrimidin-4-ones as antiplasmodial falcipain-2 inhibitors”,*Bioorganic & Medicinal Chemistry* 20, 6296-6304.

- Moln´arAnnam´aria, Anita Kapros,L´aszl´oP´ark´anyi,Zolt´anMucsi,G´aborVl´adand Istv´anHermecz, (2011), “Suzuki–Miyaura cross-coupling reactions of halo derivatives of 4H-pyrido[1,2-a]pyrimidin-4-ones”, *Organic &Biomolecular Chemistry*, 9, 6559.
- Muraglia Ester, Olaf Kinzel, Cristina Gardelli, BenedettaCrescenzi, Monica Donghi, Marco Ferrara, EmanuelaNizi, Federica Orvieto, Giovanna Pescatore, Ralph Laufer, Odalys Gonzalez-Paz, Annalise Di Marco, Fabrizio Fiore, Edith Monteagudo, MassimilianoFonsi, Peter J. Felock, Michael Rowle and Vincenzo Summa (2008), “Design and Synthesis of Bicyclic Pyrimidinones as Potent and Orally Bioavailable HIV-1 Integrase Inhibitors”,*J. Med. Chem* 51, 861-874.
- RafińskiZbigniew, Anna Kozakiewicz , and KatarzynaRafiń ska, (2014), “(−)-β-Pinene-Derived NHeterocyclic Carbenes: Application to Highly EnantioselectiveIntramolecularStetter Reaction”, *ACS Catal.*, 4, 1404−1408.
- Rahul V. Patel, Young-SooKeum, Se Won Park, (2014), “Sketching the historical development of pyrimidones as the inhibitors of the HIV integrase”, *European Journal of Medicinal Chemistry xxx*, 1 - 15.
- Rauf Abdul, SumairaLiaqat, Ashfaq M. Qureshi, Muhammad Yaqub, Aziz U. Rehman, Mahmood U. Hassan, Zahid H. Chohan, Faiz U. H. Nasim, T. Ben Hadda (2012), “Synthesis, characterization and urease inhibition of 5-substituted-8-methyl-2H-pyrido[1,2-a]pyrimidine-2,4(3H)-diones”,*Med Chem Res* 21, 60-74.
- Satyanarayana S., Praveen Kumar K., Lakshmi Reddy P., Narender R., Narasimhulu G.,Subba Reddy B. V., (2013), “ Microwave-assisted cyclocondensation: a rapid and solvent-free synthesis of 3-benzyl-2H-pyrido[1,2-a]pyrimidin-2-one derivatives”, *Tetrahedron Letters*, 54, 4892–4895

- Satyanarayana S., Praveen Kumar K., Lakshmi Reddy P., Narender R., Narasimhulu G., Subba Reddy B. V., (2013), “ Microwave-assisted cyclocondensation: a rapid and solvent-free synthesis of 3-benzyl-2H-pyrido[1,2-a]pyrimidin-2-one derivatives”, *Tetrahedron Letters*, 54, 4892–4895

- Shuanghua Hu, Yazhong Huang, Yong-Jin Wu, Huan He, Katherine A. Grant-Young, Robert L. Bertekap, Valerie Whiterock, Patrick Brassil, Kimberley Lentz, PrasannaSivaprakasam, David R. Langley, Ryan S. Westphal, Paul M. Scola, (2014), "Structure activity relationship studies of 3-arylsulfonyl-pyrido [1,2-a]pyrimidin-4-imines as potent 5-HT6 antagonists", *Bioorganic & Medicinal Chemistry*, 22, 1782–1790

- ShujiangTu, Chunmei Li, Guigen Li, Longji Cao, Qingqing Shao, Dianxiang Zhou, Bo Jiang, Jianfeng Zhouand Min Xia, (2007), "Microwave-Assisted Combinatorial Synthesis of PolysubstituentImidazo[1,2-*a*]quinoline, Pyrimido[1,2-*a*]quinoline andQuinolino[1,2-*a*]quinazoline Derivatives", *J. Comb. Chem.***,** 9, 1144–1148.
- SmetKoen De, Jan van Dun, Bard Stokbroekx, Tom Spittaels, Christine Schroyen, Peter Van Broeck, JulienLambrechts, Dirk Van Cleuvenbergen, Guy Smout, Jeroen Dubois, Andras Horvath, JurgenVerbraeken, and JefCuypers (2005), "Selectivity Control by Use of Near-IR for a Hydrogenation Process", *Organic Process Research & Development* 9, 344-347.
- SouralMiroslav, Isabelle Bouillon and Viktor Krchn, (2008), "Combinatorial Libraries of Bis-heterocyclic Compounds with Skeletal Diversity", *J. Comb. Chem.*, *10*, 923–933.
- Turco Serena Del, StefaniaSartini, Cassandra Sentieri, Chiara Saponaro,Teresa Navarra, Bianca Dario, Federico Da Settimo, Concettina La Motta,GiuseppinaBasta,(2013), "A novel 2,3-diphenyl-4H-pyrido[1,2-a]pyrimidin-4-one derivativeinhibits endothelial cell dysfunction and smooth muscle cellproliferation/activation", *European Journal of Medicinal Chemistry*, 72, 102–109.
- Vartale, S.P., Halikar, N. K., Pawar, Y.D., Tawde, K.V., (2012), "Synthesis and evaluation of 3-cyano-4-imino-2-methylthio-4H-pyrido[1,2-a]pyrimidine derivatives as potent antioxidant agents",*Arabian Journal of Chemistry.*
- VermaAbhay Kumar, Arun Kumar SinghM. Manauwarul Islam (2014), "Synthesis, characterization and evaluation of pyridopyrimidine carboxylate derivatives as potential antimicrobial and anticancer agents",*int j pharm pharmsci*,voume l6, 341-345.

- Yang Kai, Jinbao Xiang, GuochenBao, Qun Dang, and XuBai, (2013), “Synthesis of Highly Substituted 4H-Pyrido[1,2-a]pyrimidines via a One-Pot Three-Component Condensation Reaction”, *ACS Comb. Sci.,* 15, 519−524
- Yong-Jin Wu, Huan He, Shuanghua Hu, Yazhong Huang, Paul M. Scola, Katharine Grant-Young, Robert L. Bertekap, Dedong Wu, Qi Gao, Yi Li, Cheryl Klakouski and Ryan S. Westphal (2003), “Identification of a Potent and Selective5-HT6 Antagonist: One-Step Synthesis of(E)-3-(Benzenesulfonyl)-2-(methylsulfanyl)pyrido[1,2-a]pyrimidin-4-ylidenamine from2-(Benzenesulfonyl)-3,3-bis(methylsulfanyl)acrylonitrile”,*J. Med. Chem* 46 , 4834-4837.
- Yoshida Ken-ichi, Kiyoshi Nakayama, Yoshihiro Yokomizo, Masami Ohtsuka, Makoto Takemura, Kazuki Hoshino, Hiroko Kanda, Kenji Namba, Hironobu Nitanai, Jason Z. Zhang, Ving J. Leec and William J. Watkins (2006), “MexAB-OprM specific efflux pump inhibitors in Pseudomonas aeruginosa. Part 6: Exploration of aromatic substituents”,*Bioorganic & Medicinal Chemistry* 14, 8506-8518.
- YoussoufM.S., KaiserP., SinghG.D., SinghS., BaniS., GuptaV.K.,SattiN.K., SuriK.A., JohriR.K., (2008), ”Anti-histaminic, anti-inflammatory and bronchorelaxant activities of 2, 7-dimethyl-3-nitro-4H pyrido [1,2-a] pyrimidine-4-one”, *International Immunopharmacology*, 8, 1049–1055.
- Zachara John M., Calvin C. Ainsworth, Christina E. Cowan, and Berta L. Thomas, (1987), “Sorption of Binary Mixtures of Aromatic Nitrogen Heterocyclic Compounds on Subsurface Materials”, *Environ. Sci. Technol., 21,* 397-402.
- Zhang Huaihong, Rong Huang, ZhaoshengCai, ChunxiangXu, Baiwang Sun, (2013),”2-Methyl-3-chloro-9-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine Hydrochloride: Crystal Structure and Interaction with DNA”,*J ChemCrystallogr*, 43:70–75
- Al Jallo N. Hitmat and Al BiatyIbtisama, (1978), *J. Heterocyclic Chemistry*, 15, 801.