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A Review Article On Recent Advances In The Pharmacological Diversification Of Pyridine

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ABSTRACT:

Pyridine derivatives are the most common and significant heterocyclic compounds, which play an important role in various fields ranging from medical to chemo sensing applications. antioxidant, antiglycation, analgesic, antiparkinsonian, anticonvulsant, anti-inflammatory, ulcerogenic, antiviral, and anticancer activity. Furthermore, these derivatives have a high affinity for various ions and neutral species and can be used as a highly effective chemo sensor for the determination of different species. In this review article contain various biological activities, synthesis and pyridine containing drugs. Pyridine derivatives possess different biological activities such as antifungal, antibacterial, drugs. Pyridine derivatives play important role in bio-imaging applications for the diagnosis for various diseases. Pyridine-based macromolecules have greater potential for the efficient and specific delivery of drugs.

Key words; Nitrogen containing compounds, biological activities, synthesis of pyridine, pyridine containing drugs.

INTRODUCTION TO HETEROCYCLIC COMPOUNDS

Cyclic compounds having ring members atoms of at least two different elements, e.g. quinoline, 1,2 - thiazole, etc [1].

Usually, they are indicated as counterparts of carbocyclic compounds, which have only ring atoms from the same element.

"Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) begin an element other than carbon, most frequently oxygen, nitrogen, or sulfur" [2]

Heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen.[3] Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structure may consist of either aromatic or non-aromatic rings [4].

Heterocyclic derivatives can be divided into two broad areas; aromatic and non- aromatic.

1. Five-membered rings.
2. Six-membered rings.

Five-membered rings:

The five membered rings are pyrrole, furan, thiophene etc.

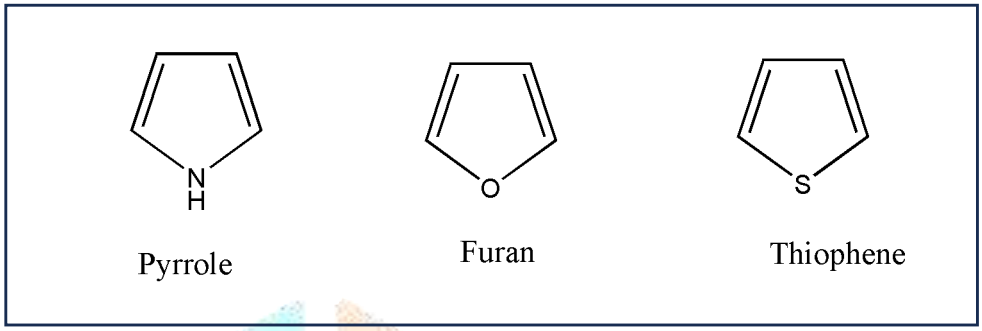


Fig 1: 5 membered heterocyclic compounds

Six-membered rings:

The six membered rings are pyridine, pyran, piperidine etc .

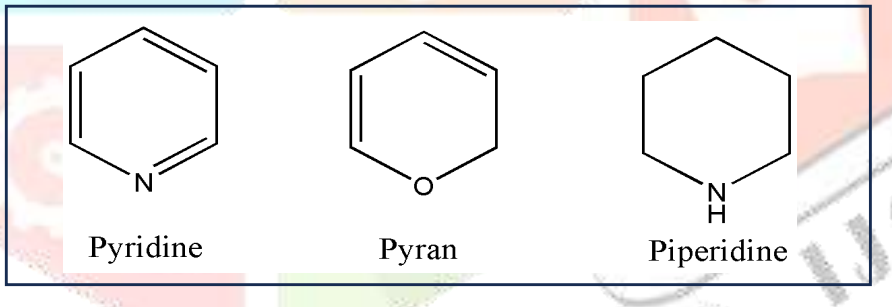


Fig 2: 6 membered heterocyclic compounds

NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS:

Heterocyclic compounds constitute the largest and most varied family of organic compounds. Nitrogen containing heterocyclic compounds are an important class of heterocyclic compounds that have paid the significant contribution towards medicinal chemistry, biochemistry, material science and also another area of science. N-heterocycles show a large number of biological activities such as antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, anti-allergic, enzyme inhibitors, herbicidal, anti-HIV, anti-diabetic, anticancer, insecticidal etc. This paper reviews the most biological active N-heterocyclic compounds which were synthesized or extracted from the plants [5].

Nitrogen-containing heterocyclic compounds are key building blocks to develop compounds of biological or medicinal interest for chemists. Heterocyclic building blocks also have important uses as components in dyestuffs, antioxidants, copolymers, bases and ligands. Most of the heterocyclic compounds which contain nitrogen show better biological activities than nonnitrogen compounds. N-containing heterocycles play a significant role for human and animal health because it is a constitutional unit of various bioactive natural products such as vitamins, hormones, nucleic acids, antibiotics, alkaloids, glycosides, haem pigments and many more compounds [6]. These N-heterocycles also occurs in anthocyanin, flavones and chlorophyll [7].

N-heterocycle is core structure in many natural drugs such as:

- Quinine
- Papaverine
- Emetine
- Theophylline
- Atropine
- Codeine
- Morphine
- Reserpine

Therefore, N-containing heterocycles are a ‘‘exclusive’’ Structures for the synthesis and development of new drugs [8]. N-heterocyclic compounds are of particular importance as they are associated with a wide variety of physiological activities. A good number of synthetic and naturally occurring N-heterocyclic systems are used in medicine, pesticides, agrochemicals, polymers etc[9] .Many N-containing heterocyclic derivatives such as indoles, imidazole’s, thiazoles, indolyl imidazole, oxadiazoles, triazoles and indazoles were marked as important bioactive and many valuable commercial products. It is therefore planned to synthesize the nitrogen-based novel heterocycles and study their pharmaceutical importance [10].

Aromaticity of pyridine:

Pyridine is a six membered heterocyclic compound with molecular formula of C_6H_5N and it is obtained from coal tar. It may be formally derived from the structure of benzene through the exchange of one ring carbon for a sp2 hybridized nitrogen a nitrogen. Pyridine is an aromatic compound, however, the nitrogen's lone pair of electrons is in an sp2 orbital orthogonal to the p orbitals of the ring, therefore it is not involved in maintaining aromaticity but it is available to react with protons thus pyridine is basic.

INTRODUCTION TO PYRIDINE:

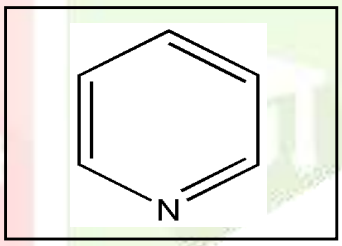


Fig 3: pyridine

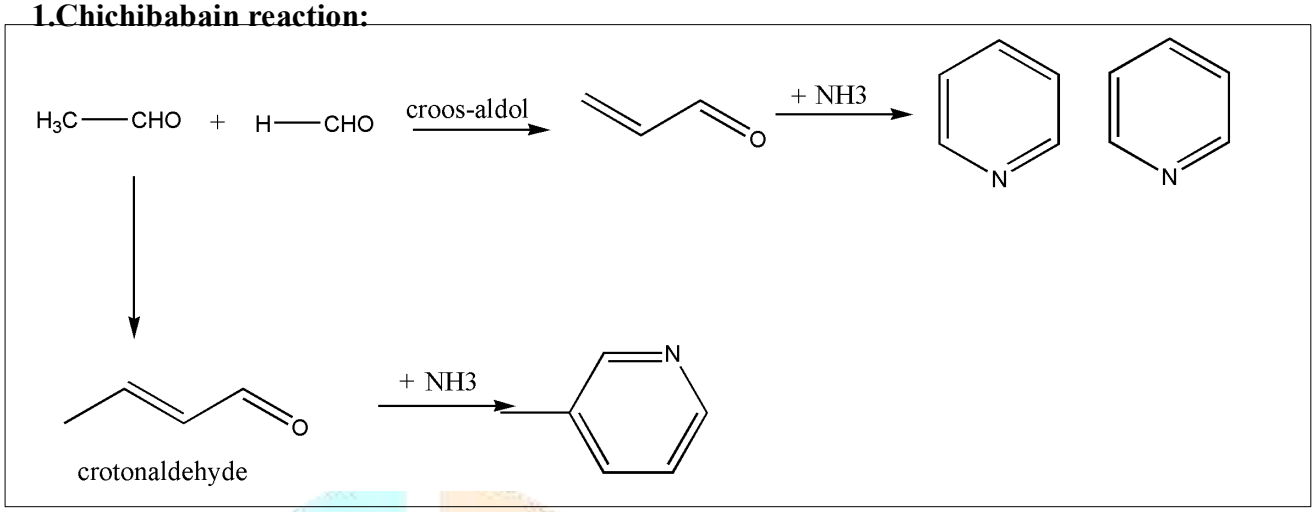
Pyridine is structurally similar to benzene, but with a nitrogen atom replacing one of the methine group. It has a six-membered ring structure with five carbon atoms and one nitrogen atom [11]. Pyridine (C_5H_5N) is a well-known primary heterocyclic organic compound and is an integral part of different natural products [12]. In several ways, it is associated with the highest fundamental and firmly established aro-mantic molecule, benzene, in which a nitrogen atom replaced one C-H group [13]. It contains six π-electrons in a conjugated system delocalized on the ring [14]. Pyridine derivatives exhibit a variety of important pharmacological activities such as antimicrobial, antimalarial, antidiabetic and anti-inflammatory activities [15]. Pyridine-related drugs have high therapeutic properties, which persuade medicinal chemists to produce many newly chemotherapeutic agents. Based on excellent biological and medicinal applications [16].

Pyridine derivatives have a greater affinity for various anions, metal cations, and neutral molecules and can be used to detects environmental pollutants in various samples (environmental, agricultural, and biological) [17]. The lone pair of nitrogen atoms within the pyridine ring plays a very important role in sensing of heavy metal ions. These compounds coordinate through the nitrogen donor atom and form a stable complex, resulting in measurable analytical signals. This property of pyridine derivatives is used in the designing of highly selective and sensitive colorimetric and fluorometric chemo sensors,[18] Pyridine derivatives also act as organ catalysts and have been applied in different reactions, The applicability of pyridine derivatives has been successfully extended to their use as starting material in organic synthetic chemistry [19]. These applications of pyridine derivatives compel chemists to introduce. novel compounds with significant applications. In this article, several pyridine derivatives have been reviewed as sensing

material for the recognition of various species (cations, anions, and neutral molecules) and their biological activities such as antifungal, antibacterial, antioxidant, antiglycation, analgesic, antiparkinsonian, anticonvulsant. Anti-inflammatory, ulcerogenic, antiviral, anticancer activity. We hope, this article will help researchers to design potent pyridine derivatives for both biological and chemo sensing applications [20].

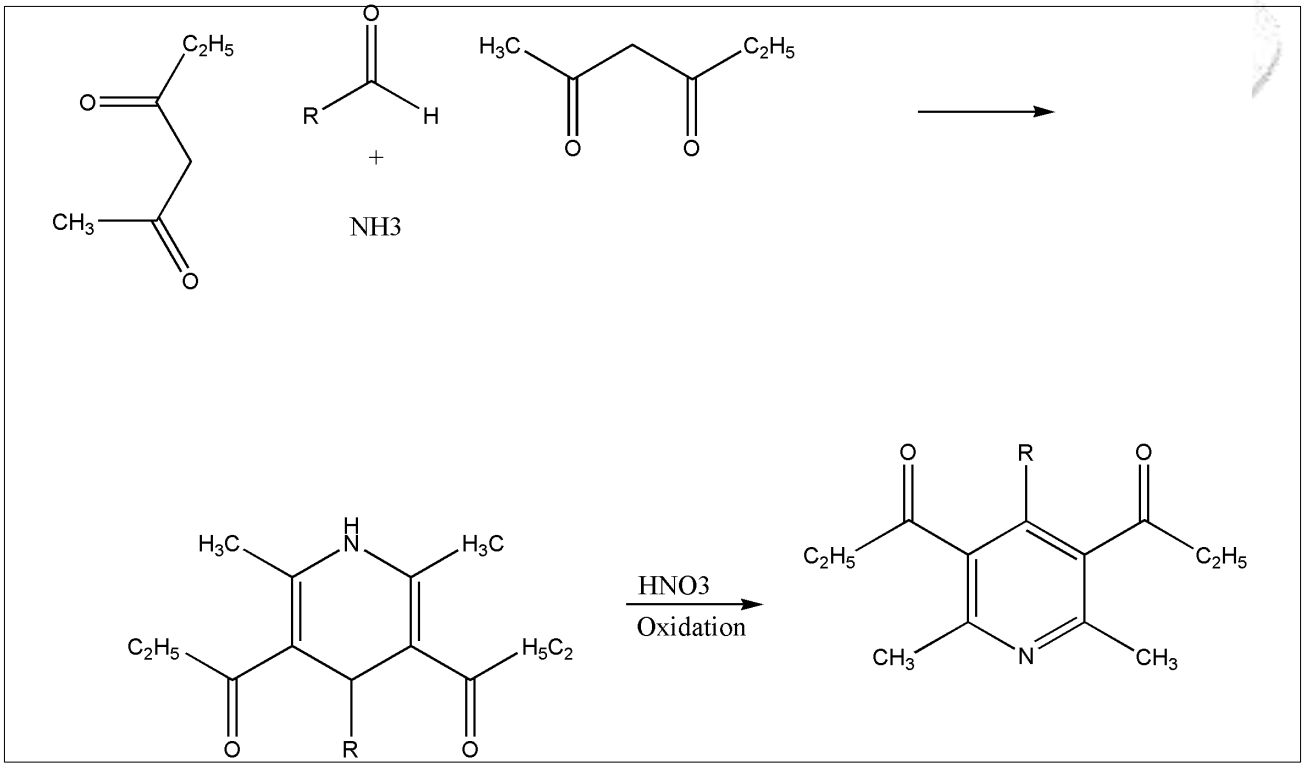
Synthesis of pyridine:

1.Chichibabain reaction:



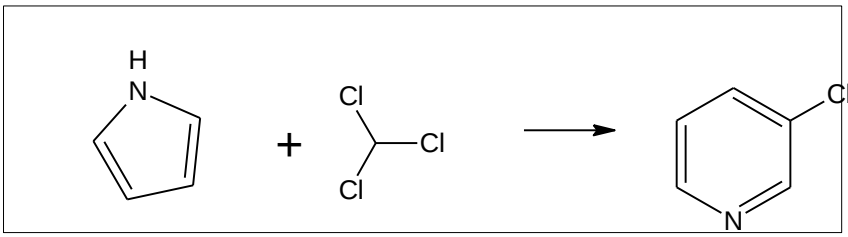
Scheme-1: synthesis of pyridine chichibabain

2.Hantzzsch reaction:



Scheme-2: synthesis of pyridine hantzzsch reaction

3.From pyrrole:



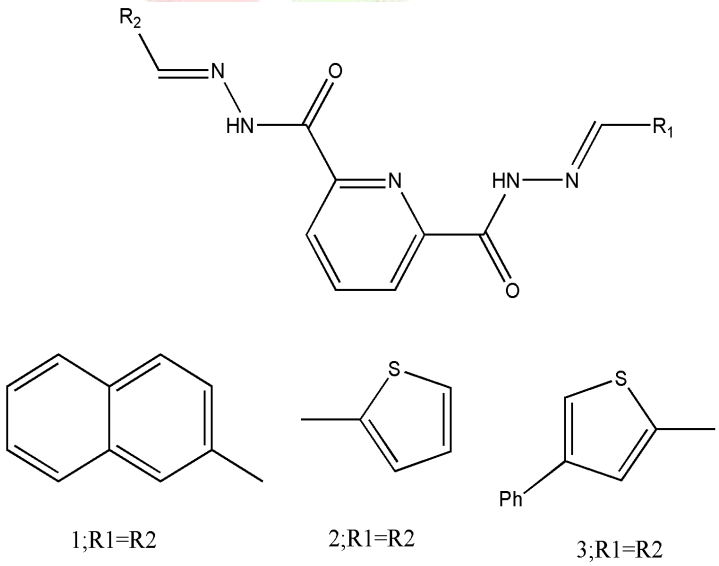
Scheme-3: synthesis of pyridine from pyrrole

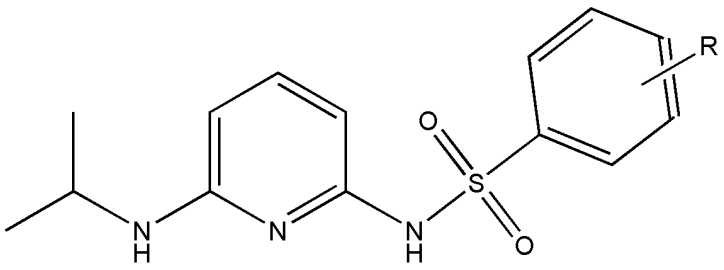
PHARMACOLOGICAL ACTIVITIES OF PYRIDINE AND IT'S DERIVATIVES:

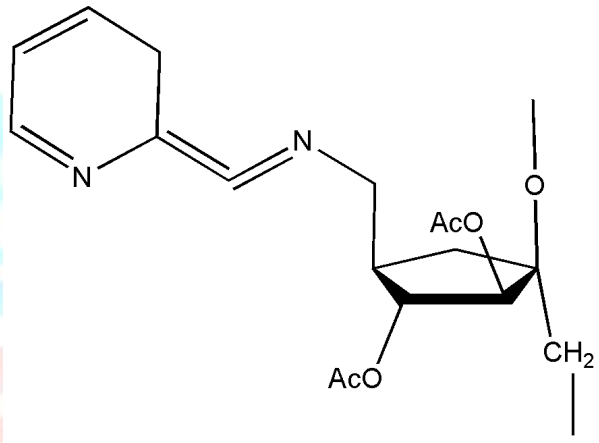
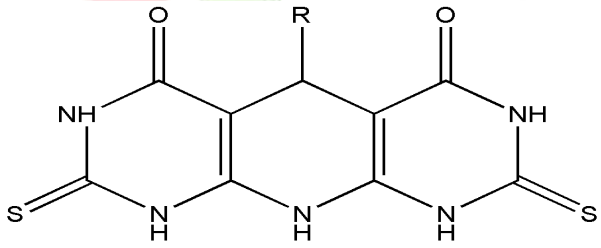
Biological Activities:

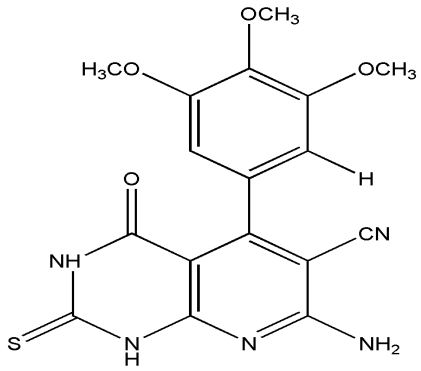
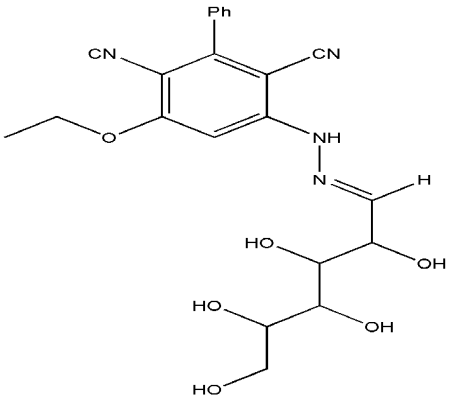
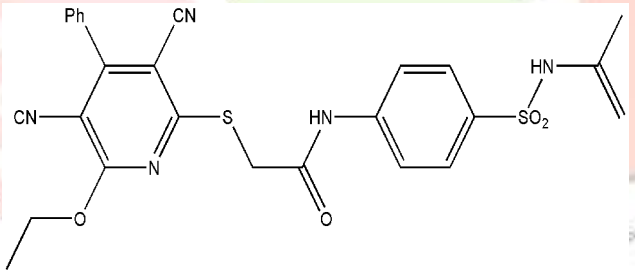
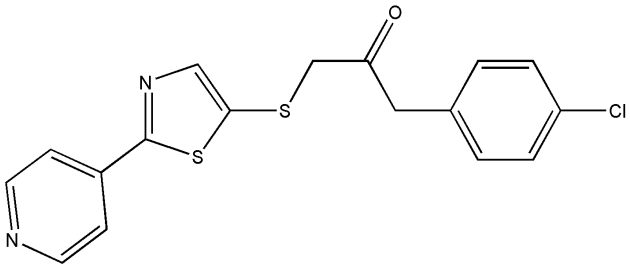
- Cytotoxic activity
- Antidiabetic activity
- Antifungal activity
- Anti inflammatory
- Anticonvulsant
- Anti-ulcer activity
- Antimicrobial activity
- Antitubercular activity
- Antimycobacterial activity
- Antiviral activity
- Anticancer activity
- Anti-Alzheimer's
- Analgesic
- Antioxidant

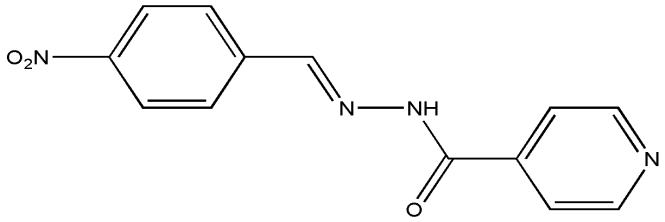
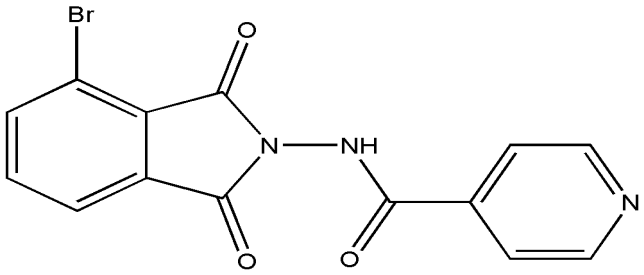
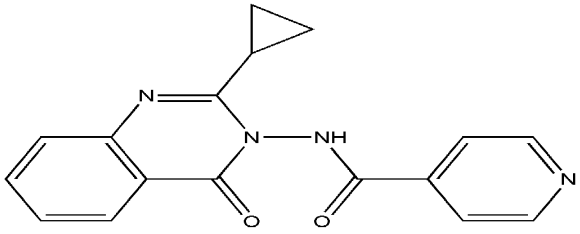
Table 1: Medically potent pyridine-based compounds against various biological activities [20]

S. No	Compound	Activity	Mechanism of action
1.	 1;R1=R2 2;R1=R2 3;R1=R2 2,6-disubstituted pyridine hydrazones	Cytotoxic activity against HT-29 cell line	Morphological changes of HT-29 and ISH cells and caspase-3 activation

2.	 R=2,6-di-F Pyridine based sulphonamide	Antidiabetic action	Inhibition of α-amylase

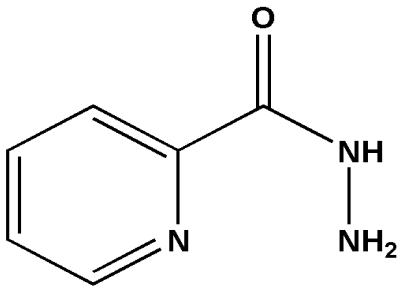
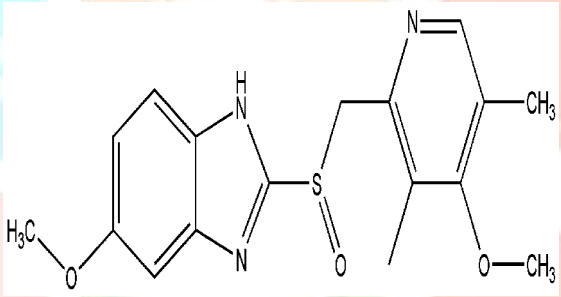
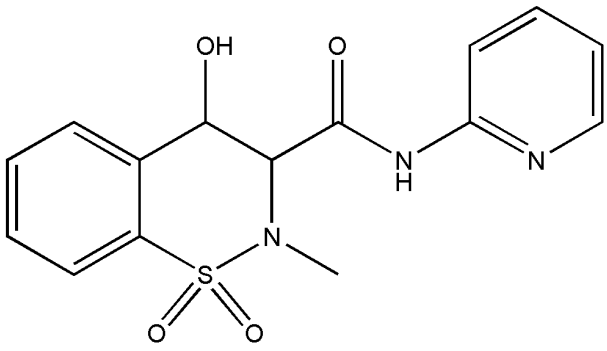
3.	 Schiff bases of inulin bearing pyridine ring	Antifungal activity	Interaction with an ionic components of the cell membranes, i.e., glucan, mannan, proteins, and lipids, to Destroy the cell membranes or To form an impervious layer Preventing the transport of essential nutrients from entering the cell
4.	 1;R=4-OH-CH4 2;R=2-OH-3-OCH3-CH3 Pyrimidine-pyridine hybrids	Anti-inflammatory activity	Competitive selective COX-2 inhibitors

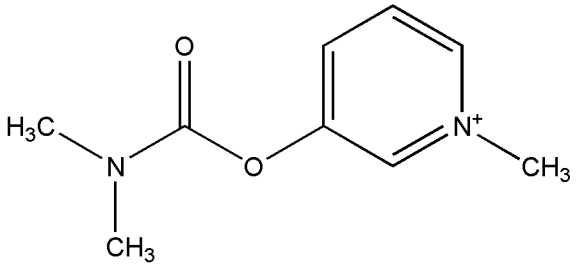
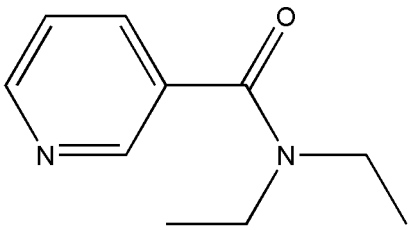
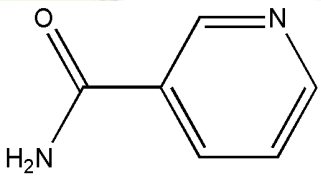
5.	 Pyrimidine-pyridine hybrids	Ulcerogenic liability	Competitive selective COX-2 inhibitors
6.	 Pyrimidine and pyridine based sulfa-drugs	Antimicrobial activity	Cell wall disruption
7.	 Pyridines and pyridine based sulfa-drugs	Antimicrobial activity	High cell permeability efficacy
8.	 Pyridinyl-thiadizole Analogues	Antitubercular activity	Inhibition of RNA synthesis

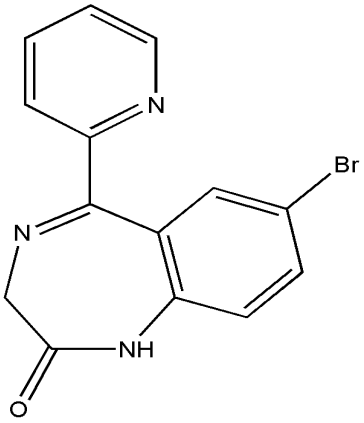
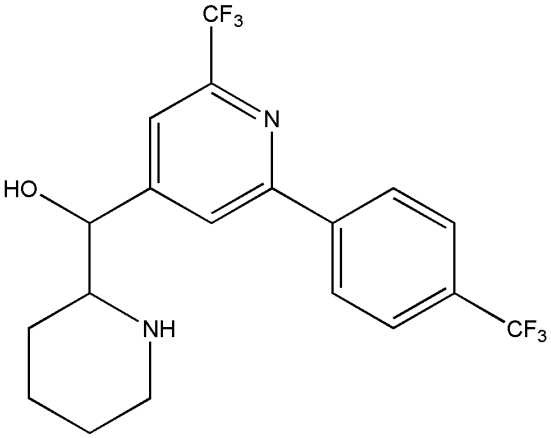
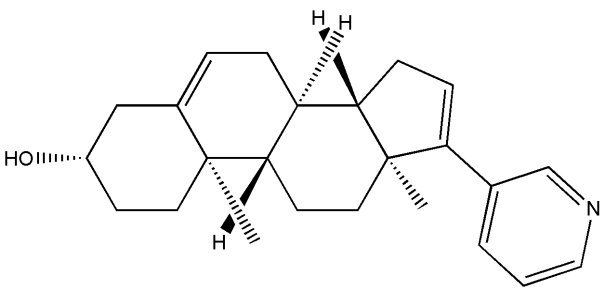
9.	 Isoniazid analouge	Antituberc ular activity	Strong binding to the DNA-Dependent RNA polymerase
10.	 Isoniazid basesd pyridine Analogues	Antimyco bacterial activity	Inhibition of RNA synthesis
11.	 Isoniazid based Pyridine Analogues	Antimyco bacterial activity	Inhibition of RNA synthesis

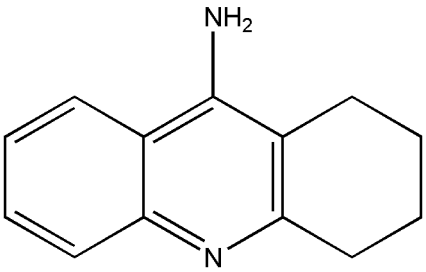
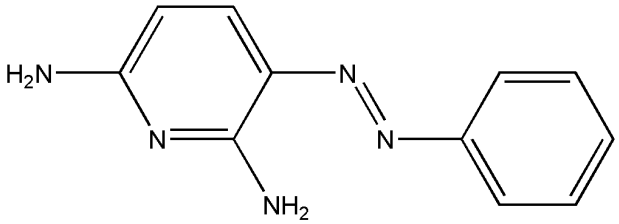
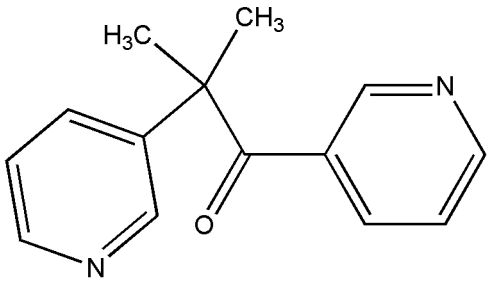
There are different examples of commercially available drugs that consist of pyridine nuclei such as Isoniazid (Antitubercular), Omeprazole (Antiulcer), Piroxicam (Arthritis), Pyridostigmine (Myasthenia Gravis), Nikethamide (Respiratory stimulant), Nicotinamide (Pellagra), Bromazepam (Anxiety), Enpiroline (Malaria), Abiraterone (Prostate Cancer), Tacrine (Alzheimer's disease), Phenazopyridine (Urinary tract analgesic), Metyrapone (NSAID),Delavirdine (HIV/AIDS), Nicorandil (Vasodilator), Doxylamine (Allergy), Tropicamide (Antimuscarinic), Nifedipine (Raynaud's syndrome), Nilvadipine(Hypertension), Roflumilast (COPD), Ciclopirox (To treat ringworm),Rimegepant (To treat migraines), Opicapone (To treat Parkinson's disease), Selpercatinib (To treat lung and thyroid cancer).

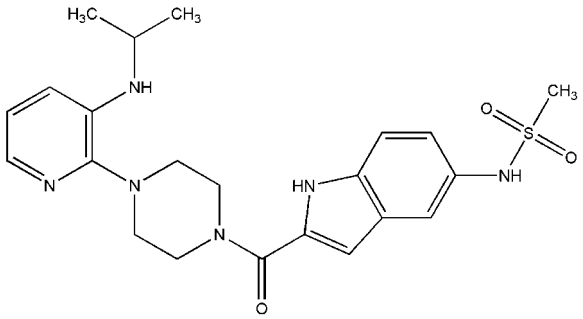
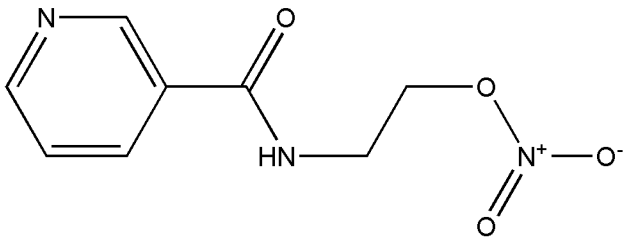
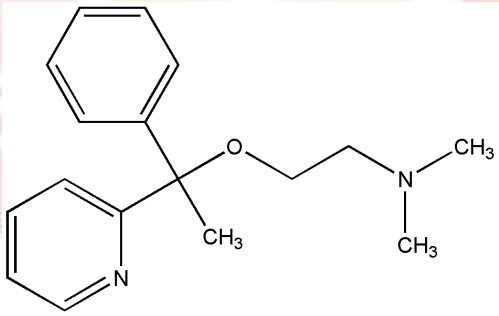
Table: 2 list of drugs and their uses contains pyridine nucleus in their structure

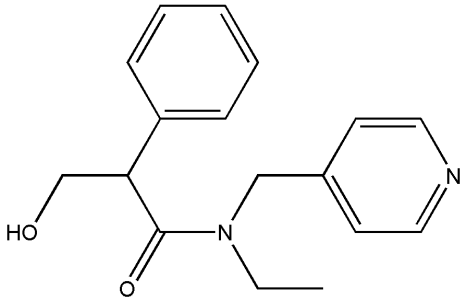
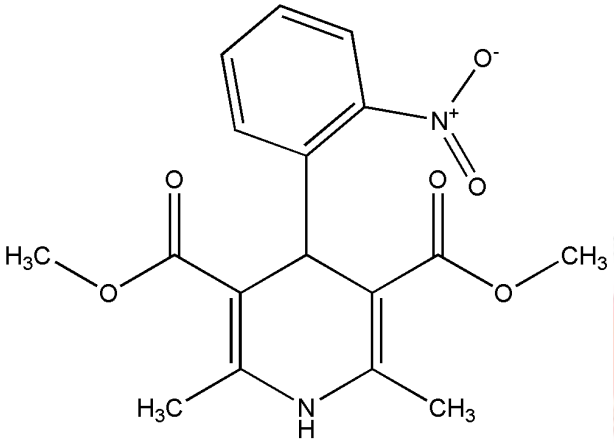
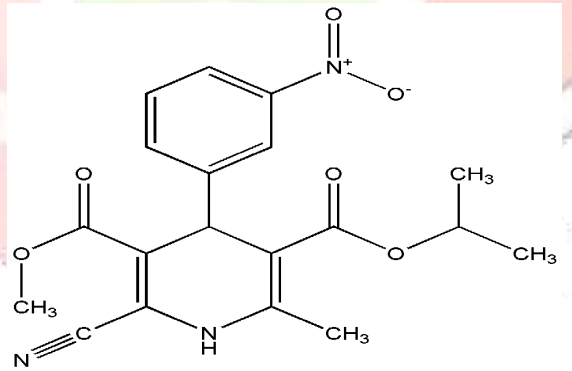
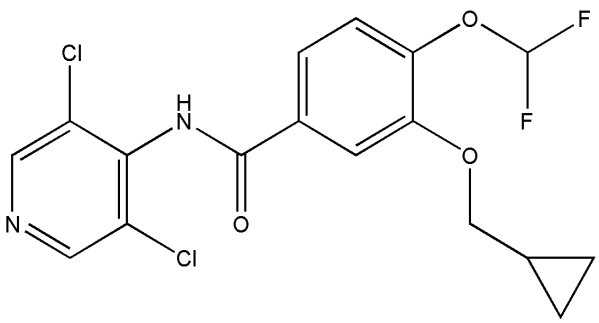
S.NO	DRUG	STRUCTURE	BRAND	USES
1.	Isoniazid		Nydrazid	Antitubercular
2.	Omeprazole		Prilosec and Losec	Antiulcer
3.	Piroxicam		Flexar	Arthritis

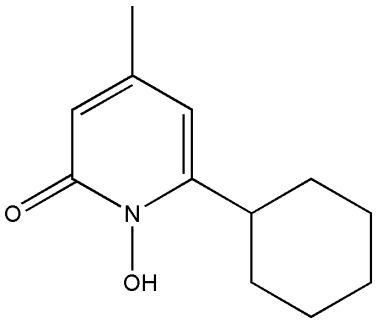
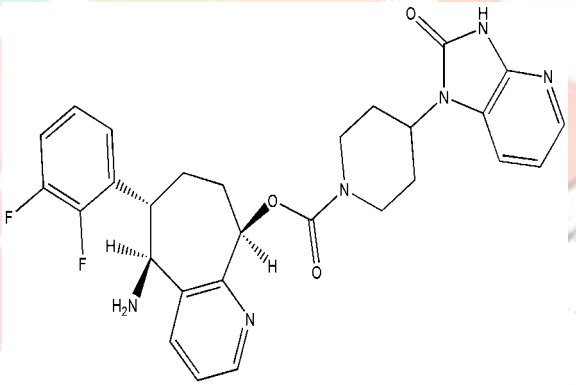
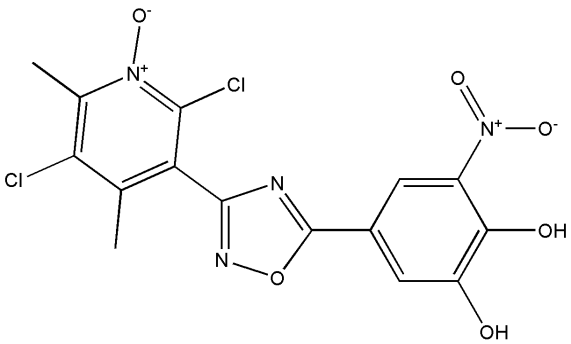
4.	pyridostigmine		Mestinon	To treat myasthenia gravis
5.	Nikethamide		Coramine	Respiratory stimulant
6.	Nicotinamide		Freederm, Niatin, Nicam	Pellagra

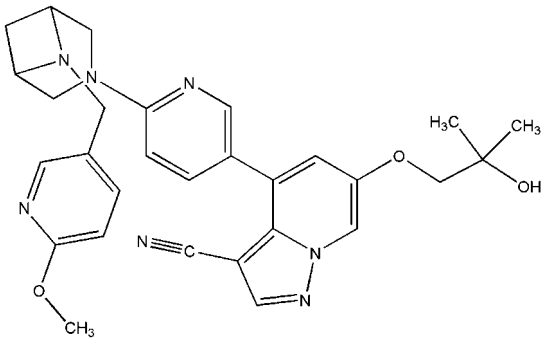
7.	Bromazepam		Lectopam, Lexotan, Lexilium, Brazepam	Anxiety
8.	Enpiroline		-	Malaria
9.	Abiraterone		ZYTIGA	Prostate cancer

10.	Tacrine		Cognex	Alzheimer's disease
11.	Phenazopyridine		Pyridium	Urinary tract analgesic
12.	Metyrapone		Metopirone	NSAID

13.	Delavirdine		Rescriptor	HIV/AIDS
14.	Nicorandil		Necomax	Vasodilator
15.	Doxylamine		Unisom	Allergy

16.	Tropicamide		Mydriacyl, Tropicacyl	Antimuscarinic
17.	Nifedipine		Adalat, Adipine, Nifedipress	Treat Raynaud's syndrome
18.	Nilvadipine		Nilvad, ARC029	To treat hypertension
19.	Roflumilast		Daxas	Treat COPD

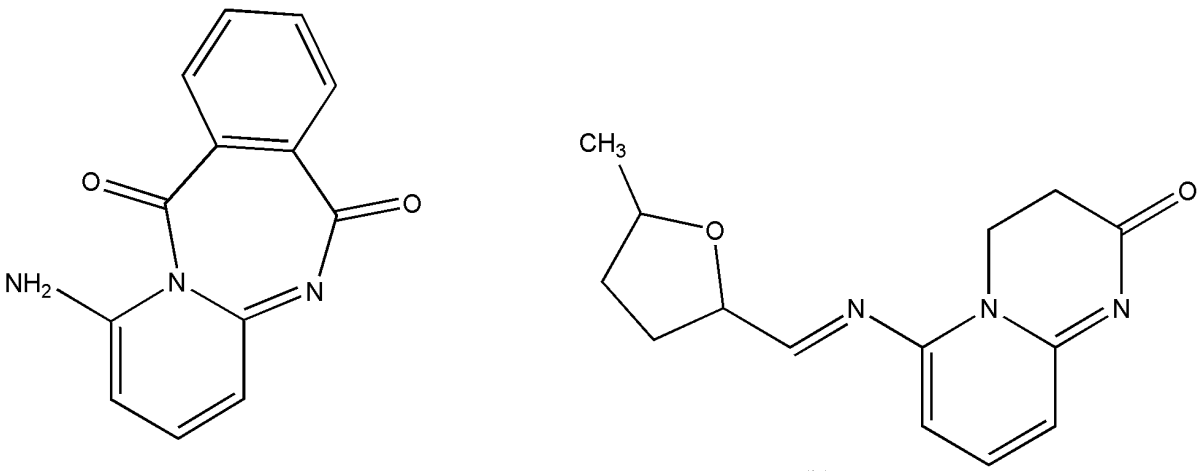
20.	Ciclopirox		Loprox, Penlac	To treat ringworm
21.	Rimegepant		Nurtec, ODT	To treat migraines
22.	Opicapone		Ongentys	To treat Parkinson's disease

23.	Selpercatinib		Retevmo	Treat lung and thyroid cancer

PHARMACOLOGICAL ACTIVITIES OF PYRIDINE AND IT'S DERIVATIVES:
1.ANTICANCER ACTIVITY:

It is challenging work for researchers to develop more effective and efficient chemotherapy treatments, and it is also noted that the drugs that are currently on the market are not up to par. By measuring a compound's capacity to inhibit the uncontrollably high rate of cell division, anticancer activity is ascertained using the 3-(4,5-dimethylthiazole-2-yl)-2, 5-diphenyltetrazolium bromide (MTT). Since pyridine derivatives are most promising options for treating many cancers, chemist and biochemist have been designing new pyridine derivatives to provide stop the spread of cancer by blocking the enzymes that cause the corresponding diseases [21].

Bassyouni et al. synthesized a large number of pyridine-derived compounds **a, b,** and evaluated the cancer growth-inhibitory potency of these derivatives in liver HEPG2cell lines. Comparing these chemicals to the well-known anticancer medication 5-fluorouracil (5-FU) and doxorubicin (DOX), a preliminary screening test revealed a moderate to significant growth suppression action on the cancer cells. The cytotoxic activity of **5**-FU and DOX, two conventional anticancer medications, was compared to that of the investigated chemicals **a, b,** are the more active and exhibit reasonable growth inhibition as compare to 5-FU and DOX [22].



(a) (b)

Fig 4: anticancer activities of pyridine derivatives

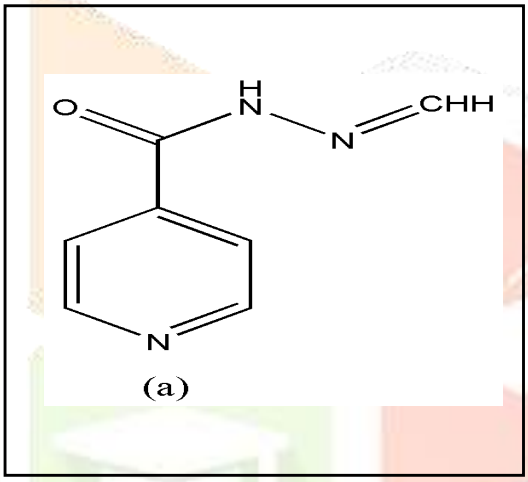
2.ANTI-TUBERCULAR ACTIVITY:

Mycobacterium tuberculosis is the primary cause of TB. The difficulties in eradicating tuberculosis (TB) globally have increased with the introduction of DR-TB (drug resistance TB), MDR-TB (multidrug-resistance TB), XDR-TB (extensively drug-resistance TB) and TDR-TB (fully resistance TB). Frontline anti-TB medications are pyridine-derivatives chemicals; nevertheless, bacterial stains resistance to isoniazid (INH) are sadly becoming more prevalent. Therefore, it appears that INH compounds with higher lipophilicity are among the most promising anti-TB drugs.

Dandawate et al. synthesised a plumbagin-isoniazid analog and its inclusion complex with beta-cyclodextrin fallowed by evaluation [23].

For their antitubercular activity under low and high iron conditions. The MIC values of the standard isoniazid drug 0.125 and 32µg/ml. In addition, the β-cyclodextrin complex showed better thermal stability and aqueous solubility.

Hearnaet et al. reported the lipophilic adaptations of the structurally modified frontline antitubercular pyridine-derived isonicotinic acid hydrazide drug **(a)** in which the hydrazine moiety is protected by N2-acetylation using N-arylaminoacetyl transferases. These compounds showed excellent activity against M. Tuberculosis and tuberculosis-infected macrophages [24].



(a)

Fig 5: anti-tubercular activity of pyridine derivative

3.ANTI BACTERIAL ACTIVITY

Sarova et al. synthesized three dodecanoic acid derivatives, **(a),** and evaluated their antibacterial activity. E. coil, S. aureus, and B. subtilis. They have also antifungal activity against C. albicans and A. Niger [25].

Narang et al. synthesized nicotinic acid benzylidene hydrazide derivatives and evaluated their antimicrobial activity. The antimicrobial screening indicated antimicrobial activity that compounds with nitro and dimethoxy substituents have better antibacterial activity against B subtilis, S. aureus, E coli, A. Niger, and C. albicans). Some of these have antimicrobial activity comparable to that of the fluconazole and norfloxacin standard drugs [26].

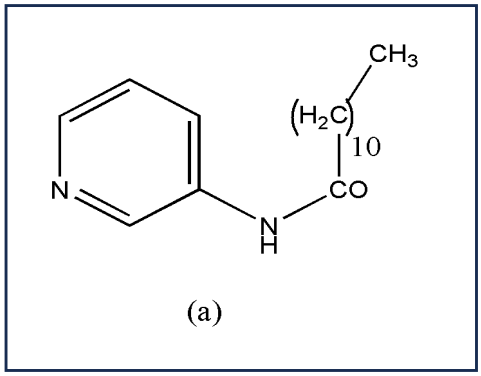


Fig 6: antibacterial activity of pyridine derivative

Malhotra et al. synthesized Mannich basesa-j using a classical Mannich reaction and evaluated their antibacterial activity. The compounds e, h, I, and j (MIC value of 6.25 – 12.5µg/ml.) show better antibacterial activity than other compounds against Gram-positive (S. aureus and B. subtilis) and Gram-negative (E. coli and P. aeruginosa) bacteria. Interestingly, these compounds also showed good [27].

4.ANTI VIRAL ACTIVITY

One of the most dangerous illnesses is viral infections, and the antiviral chemotherapy drugs now on the market are insufficiently effective in the clinic, which causes fatalities and other severe illnesses in people. A family of substances known as antiviral medicines is utilized to treat various viral illnesses. Thus, it is imperative to discover innovative antiviral candidates, as they are crucial medications aim to stop the development of certain viruses. Pyridine derivatives are a great class of chemical molecules to work with for creating new and potent antiviral medications [28].

Balzarini et al. synthesized pyridine N-oxide derivatives **a**, **b**, and the activity of these compounds was evaluated against SARS and feline coronavirus. Interestingly it was found that compounds a and b have potential activity against SARS-CoV and feline coronavirus strain.

Ghosh et al. synthesized 5-chloro-4-methylpyridin-3-yl-1H-indole -4-carboxylate ('d' in) and evaluated its antiviral activity. An interesting result was observed by Compound d, which showed good antiviral activity (EC_{50}~ 2.2 µM) against SAS-CoV-23CLpro and is comparable to that of Remdesivir. The antiviral activity of the compound is not due to cytotoxic effects but because of the destructive "antiviral effect [29].

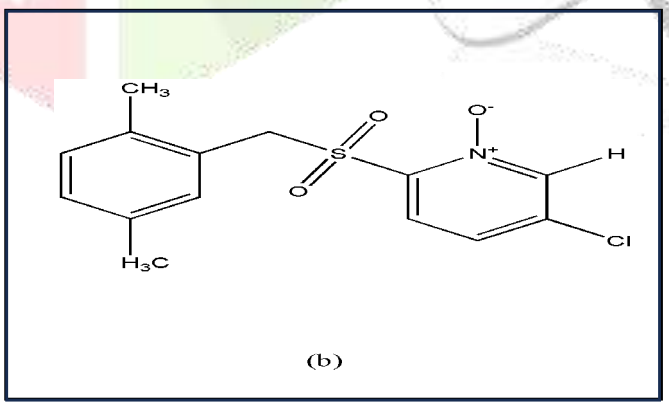


Fig 7: antiviral activity of pyridine derivative

5.ANTI MICROBIAL ACTIVITY:

In developing countries, nearly one-third of the number of total deaths per year is caused by infectious disease. Different diseases are caused by different types of microorganisms. The existing anti-microbial drugs are not very effective for many microorganisms [30].

Bark et al. have reported series of pyridopyrimidines **(a), (b)** evaluate their antibacterial activity against Staphylococcus aureus and Bacillus subtilis, utilising ampicillin standard [31]

The anti-bacterial activity was evaluated against Mycobacterium tuberculosis H37Rv. ***Elumalati et al***. have reported a novel pyridine-derived compound. Which shows the anti-microbial against gram positive bacteria (B. subtilis), gram-negative bacteria (E. coli), M tuberculosis (H387Rv) and M tuberculosis (CIP) [32,33,34].

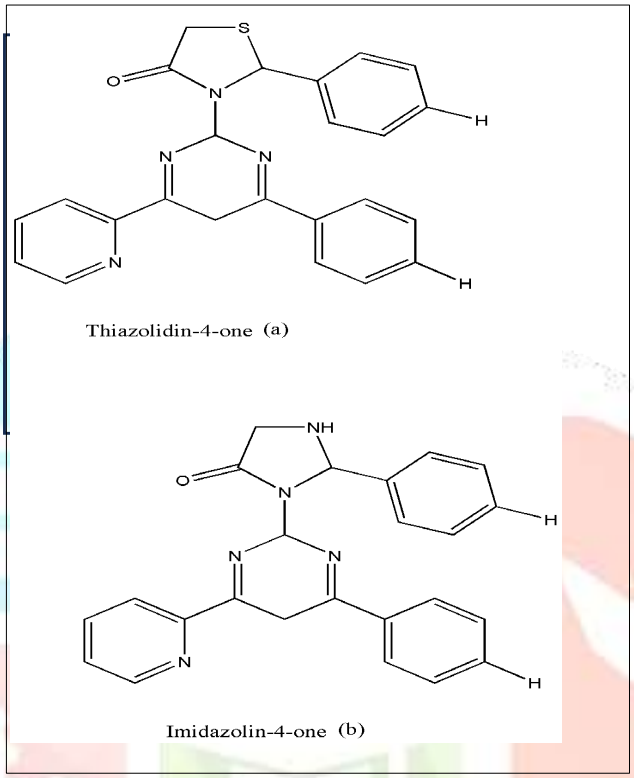


Fig 8: antimicrobial activity of pyridine derivatives

6.ANTI DIABETIC ACTIVITY:

Type 1 diabetes mellitus (T1DM) can be produced with Streptozotocin (STZ) by the pancreatic islet β-cell destruction. Type 2 diabetes models are also going to developed using (Streptozotocin) STZ. Several animals' species e.g. the monkey, rat, and mouse, are more sensitive to the pancreatic β-cell cytotoxic effects of STZ compared to a rabbit. Animals such as rats and mice are being used for assessing the pathological consequences an potential therapies/treatments in diabetes patients. ***Bahekar et al.*** reported two sets of pyrrole-based pyridine derivatives and thieno-based pyridines, respectively **(a), (b).** All the compounds exhibit in vitro glucose-dependent insulinotropic activity towards RIN5F cell lines. Kim et al. reported the synthesis of a few thiazolidinedione-based pyridines compounds and showed the hypoglycemic activity and hypolipidemic activity of the synthesised compounds [35].

Ma et al. synthesised a new class of complexes of thieno-pyridine derivatives, which act as gluconeogenesis inhibitors that are found to be effective in type 2 diabetes mellitus [36].

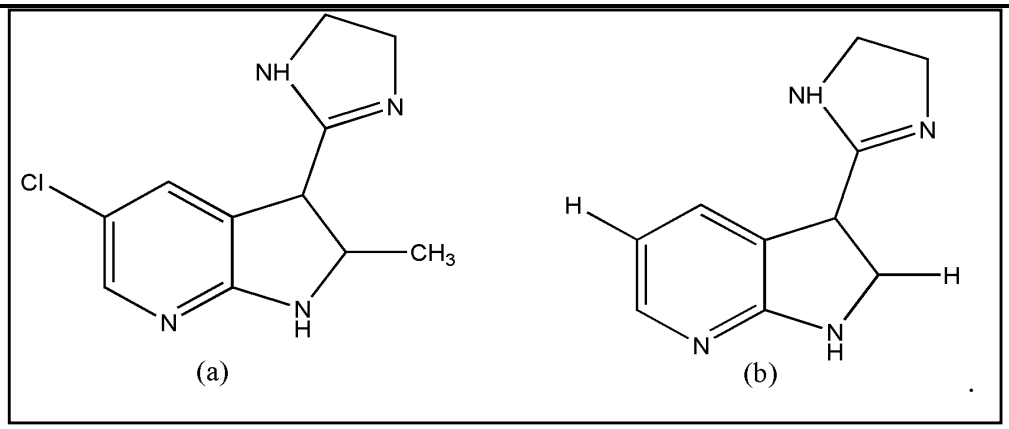


Fig 9: anti diabetic activity of pyridine derivatives

7.ANTI FUNGAL ACTIVITY:

Ozdermi et al. reported a group of eight novel pyridine derivatives showing antifungal activity when exposed a panel of ten human pathogenic candida species (Fig 1) exhibiting strong inhibition (MIC 0.016 mg ml^{-1}. Against the screened candida species.

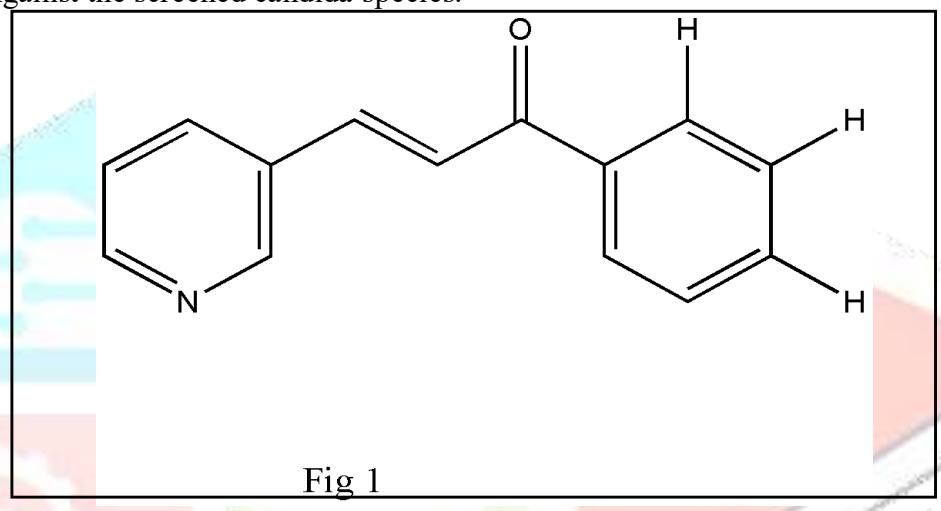


Fig 10: antifungal activity of pyridine derivative

The obtained quaternized pyridine derivatives of betulin triterpenes showed good antibacterial and antifungal activities compared to the initial compounds [37].

8. ANALGESIC, ANTIPARKINSINIAN AND ANTICONVULSANTS ACTIVITY:

Analgesics are substances used to relieve pain without loss of consciousness. There various sources of analgesic drugs such as medical plants like Urtica dioica, Andrographis Paniculata, Bunts longifolia, MorindaCitrifolia, AloeveraBarbedensis, Curcuma alismatifolia, and synthesised compound like Paracetamol, Ibuprofen, Diclofenac, etc. some pyridine derivatives also possessed significant analgesic activity. For e.g. the analgesic activity of pyridine derivatives [38]. Were screened for analgesic activities using formalin induced test, tail- flick test and hot- plate test. The novel series of pyridine derivative containing thiazole moiety were synthesised and screening for their anti-analgesic, anti-inflammatory, anticonvulsant, antiparkinsonian activities. The potency of these compounds was to compared to reference drugs such as diclofenac, benztropine, potassium, carbamazepine. The analgesic activities of all the tested compounds were more potent than the reference drug (valdecoxib) [39].

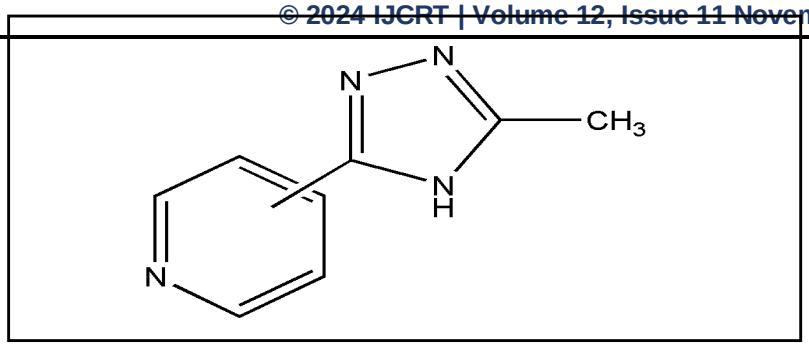


Fig 11: analgesic, antiparkinsinian and anticonvulsant activities of pyridine derivative

9.ANTIOXIDANT AND ANTIGLYCATION ACTIVITY:

The novel series of pyridine derivatives bearing imidazole (a) were designed and synthesised. These compounds were studied for their antioxidant and antiglycation activities [40]. Among these compounds was found to be the most active compound. These compounds (b) also exhibited better activity. A series of insulin derivatives containing pyridine ring were synthesised and tested for their antioxidant potential against DPPH*, hydroxyl (OH$^{*)}$, and superoxide (O_2^{*}) radicals, respectively. These compounds are significant improvement on scavenging DPPH* and OH*. Which can scavenge the OH* radical completely at 0.4mg/ml. The scavenging activity of compound O*was among all the screened compounds [41].

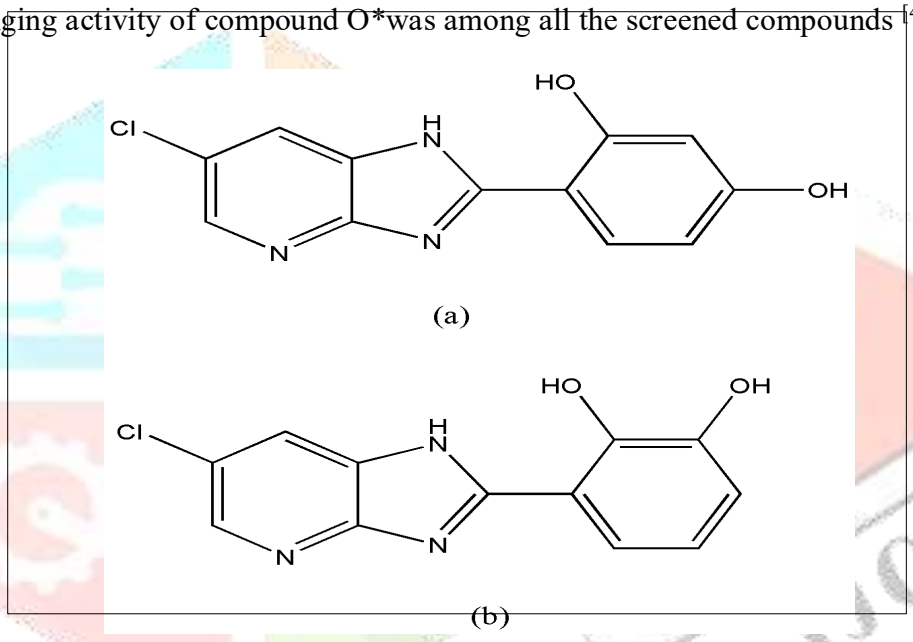


Fig 12: antioxidant and antiglycation activity of pyridine derivative

10.ANTI-INFLAMMATORY AND ULCEROGENIC ACTIVITIES:

Inflammatory is a common condition that makes the body redden and swollen due to some infections or injuries. Different pyridine have significant anti-inflammatory activities.

Some novel pyrimidine-pyridine hybrids (a) and (b) were designed and synthesised. These synthesised compounds were tested for their anti-inflammatory and ulcerogenic activities. The results showed that compounds (c) exhibited potent activity with edema (Inhibitory percent=74% after 1h). compounds having electron-donating (ED). Furthermore, the compounds and showed better COX-2 inhibitory activity (IC_{50}=0.25-0.89Mm) than the celecoxib (IC_{50}=1.11Mm). Ulcerogenic studies showed that these compounds exhibited comparable ulcerogenic activities to celecoxib but less than indomethacin [42].

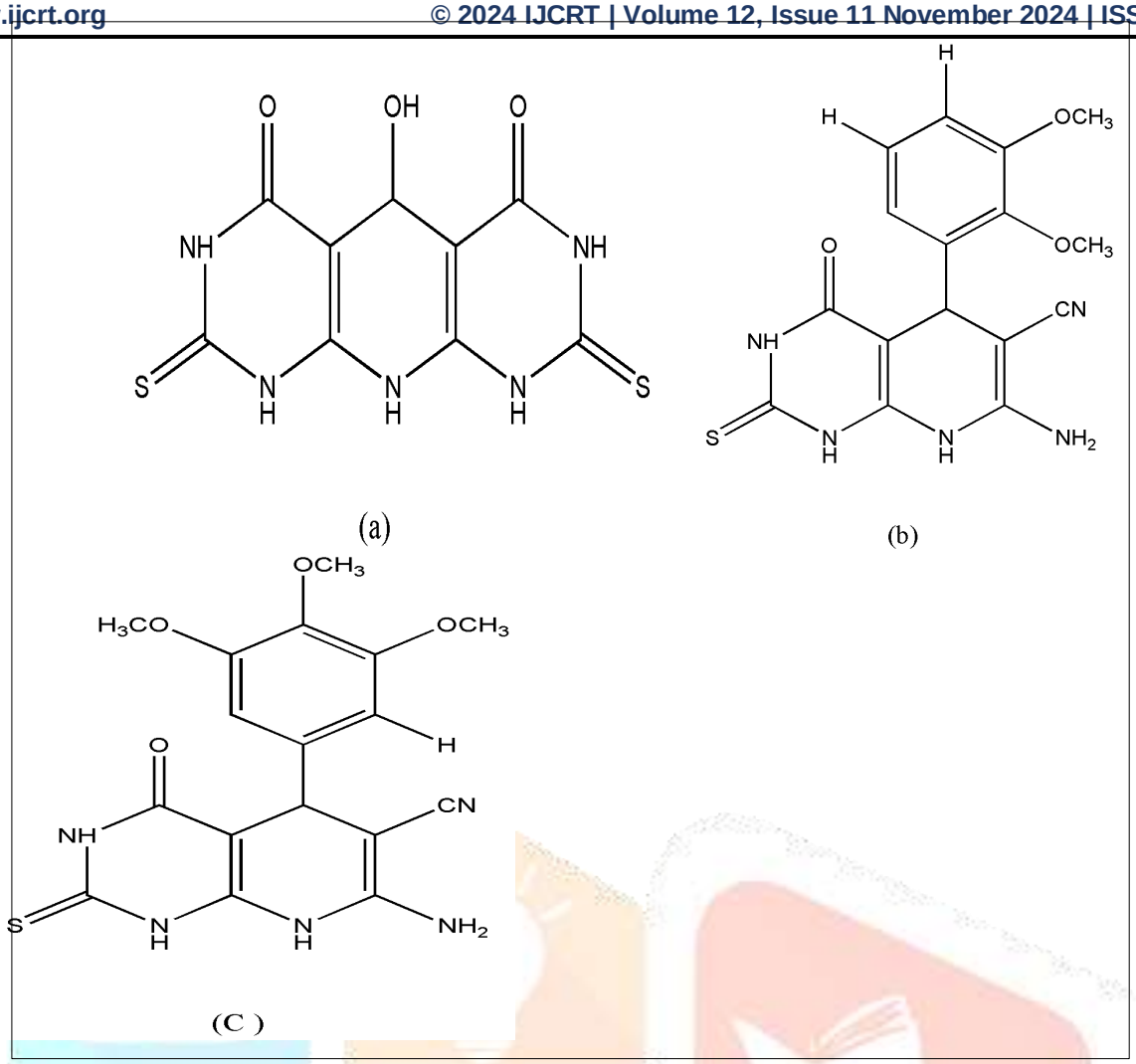


Fig 13: anti-inflammatory and ulcerogenic activity of pyridine derivative:

CONCLUSION: This review summarizes the synthesis and medical applications of pyridine and its derivatives. Pyridine and its derivatives have many biological activities such as anti-bacterial, anti-fungal, anti-viral, analgesic, anti-diabetic, and anti-cancer, anti-inflammatory, anti-convulsant, anti-ulcer activity, anti-microbial activity, anti-tubercular activity, anti-oxidant, analgesic. The biological activity of a drug depends largely on its physico-chemical property. pyridine derivatives also play an important role in bio-imaging applications for diagnosing various diseases. The presence of pyridine along with other groups like imidazole, benzimidazole, pyrimidine, and p-chlorobenzoyl, moieties help to show better pharmacological activity.

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Regd. No: 21ER1R0050

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