CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.21890790

Available online at: http://www.iajps.com Review Article

PYRIDINE: A PROMISING AND VERSATILE NUCLEUS FOR DRUG DISCOVERY

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Abstract:

Pyridine is an important nitrogen containing heterocyclic compound which plays an important role in medicinal chemistry because of its various biological activities. This review summarizes the chemistry, synthesis, chemical reactions and pharmacological importance of pyridine derivatives. It highlights the reported antimicrobial, antibacterial, antitubercular, antiviral and anticancer activities of pyridine derivatives and demonstrates the importance of structural modifications of pyridine ring to improve biological efficacy. Special emphasis is given to the antitubercular potential of pyridine derivatives as several compounds have shown promising activity against Mycobacterium tuberculosis including drug resistant strains. The review also provides examples of marketed drugs containing the pyridine ring highlighting its importance as a versatile pharmacophore in drug discovery. In general, the literature indicates that pyridine derivatives have broad therapeutic potential and continue to be useful scaffolds for the development of new and more effective medicinal agents.

Keywords: *Pyridine, Heterocyclic compounds, Medicinal chemistry, Drug discovery, Biological activity.*

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Please cite this article in press Sandhya D C et al., Pyridine: a promising and versatile nucleus for drug discovery, Indo Am. J. P. Sci, 2026; 13(08).

INTRODUCTION:

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is one of the most serious infectious diseases in the world. It remains a major public health challenge despite available treatments. The rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has made current therapies less effective and has increased mortality rates [1, 2] Traditional anti-TB therapy involves long treatment with first-line drugs like isoniazid, rifampicin, ethambutol, and pyrazinamide, which often results in poor patient adherence and the development of resistance[3]. This creates an urgent need for new, effective, and safer antitubercular agents [2].

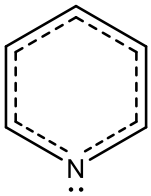
In recent years, heterocyclic compounds, especially those containing nitrogen, have attracted attention in medicinal chemistry for their wide range of biological activities [4]. Pyridine and its derivatives are highly promising due to their favourable properties like polarity, solubility, and ability to form hydrogen bonds, which improve drug–target interactions [5]. The pyridine structure is also present in several drugs, including anti-TB agents like isoniazid, underscoring its role as an important component in drug design [6].

Structural modifications of pyridine derivatives have led to compounds with strong antimycobacterial activity against both drug-sensitive and resistant strains of *M. tuberculosis*[1, 2]. Studies show that adding different functional groups or combining them with other active substances increases their effectiveness and selectivity [7]. Furthermore, pyridine-based compounds display a wide variety of biological activities, including antibacterial, antifungal, antiviral, and anti-inflammatory effects, making them versatile candidates in drug discovery [5].

This review highlights the anti-tubercular potential of pyridine derivatives, focusing on their synthesis, structural diversity, and biological activity. Understanding these aspects may help in developing new therapeutic agents to fight resistant TB and improve global health outcomes.

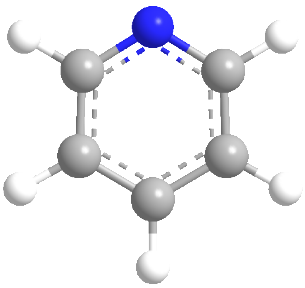
CHEMISTRY OF PYRIDINE COMPOUNDS

Mononitrogen containing a six-membered heteroaromatic compound structurally similar to benzene with the molecular formula C_5H_5N is named pyridine. This simplest and most common compound is water-miscible, flammable, and colourless to yellow liquid.[8–10]



pyridine

1



2

PHYSICAL PROPERTIES

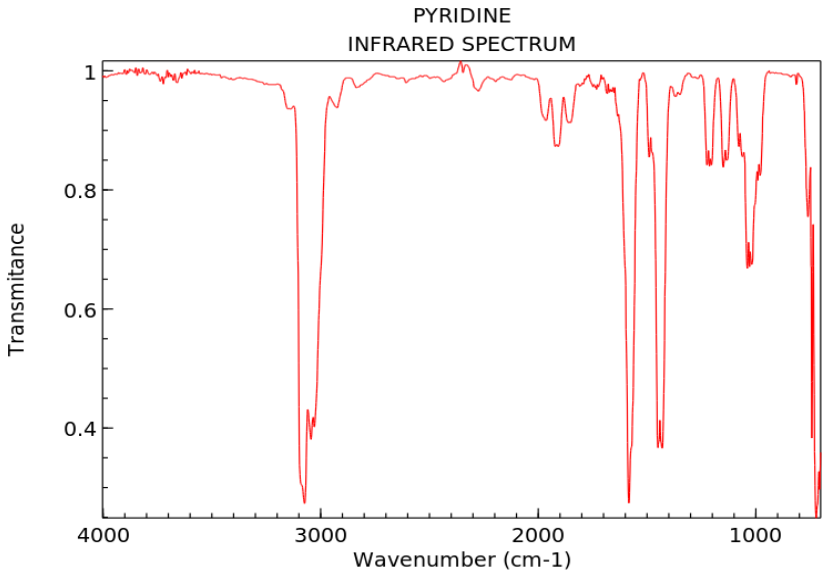
Chemical Name	**Pyridine**
Molecular Formula	**C_5H_5N**
Synonyms	**Azine, Azabenzene, Mononitrogen benzene**
Molecular Weight	**79.10 g/mol**
Physical State (Form)	**Liquid**
Appearance/Colour	**Colourless to pale yellow**
Odour	**Unpleasant/pungent**
Boiling Point (BP)	**~115.5 °C**
Melting Point (MP)	**~ −41.6 °C**
Density	**~0.978 g/cm³**
Vapour Pressure	**Moderate (volatile liquid)**
Refractive Index	**~1.509**
Flash Point	**~20 °C (flammable)**
Solubility	**Miscible with water and organic solvents**
Water Solubility	**Completely miscible**
pKa (conjugate acid)	**~5.2**
Basic Nature	**Weak base**
Hydrogen Bonding	**Acts as H-bond acceptor**
Flammability	**Highly flammable liquid**
Toxicity	**Moderately toxic, irritant**

SPECTROSCOPIC FEATURES

IR SPECTRA:[11]

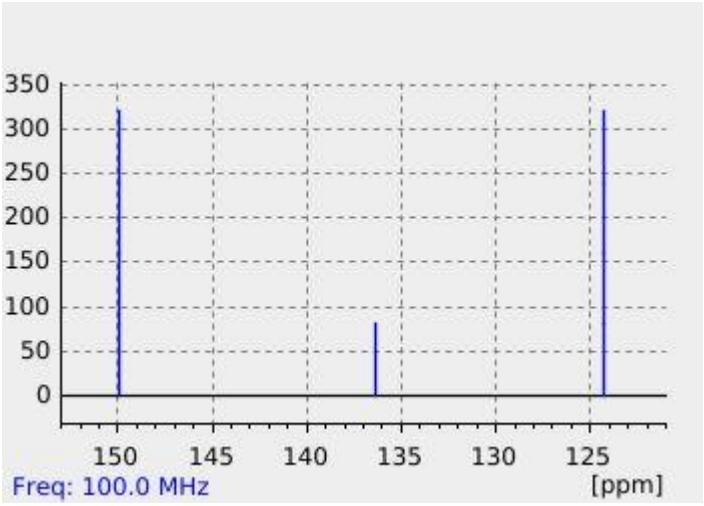
This IR spectrum belongs to pyridine (C_5H_5N). We can see aromatic C–H stretching around 3000–3100 cm^{-1} and strong ring vibrations near 1600–1500 cm^{-1}. The peaks between 1400–1000 cm^{-1} are due to C–N and ring stretching, while signals below 900 cm^{-1} come from out-of-plane C–H bending, confirming its heteroaromatic ring structure.

NMR



SPECTRA:[12]

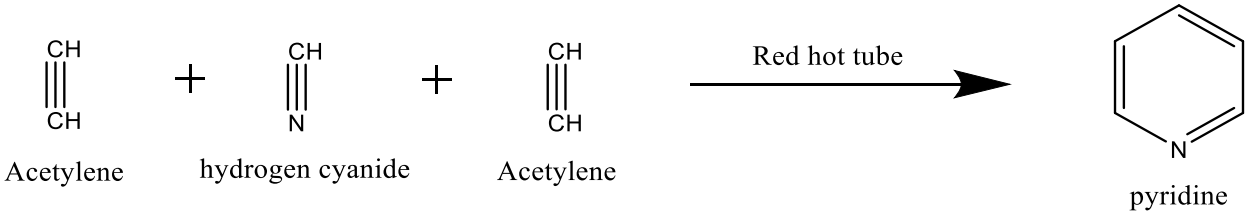
This ^{13}C NMR spectrum of pyridine shows three peaks at around 150, 136, and 123 ppm, reflecting three distinct carbon environments in the ring. The signal near 150 ppm corresponds to carbons close to the nitrogen, which appear downfield due to deshielding. The other two peaks arise from the remaining aromatic carbons.



METHODS OF SYNTHESIS OF PYRIDINE

1. **Bonnemann Cyclization**

This involves the use of an essence complex catalyst to form pyridine derivations. The Bönnemann cyclization refers to the trimerization process involving a section of a nitrile segment and two pathways of acetylene, resulting in the formation of pyridine.[13]

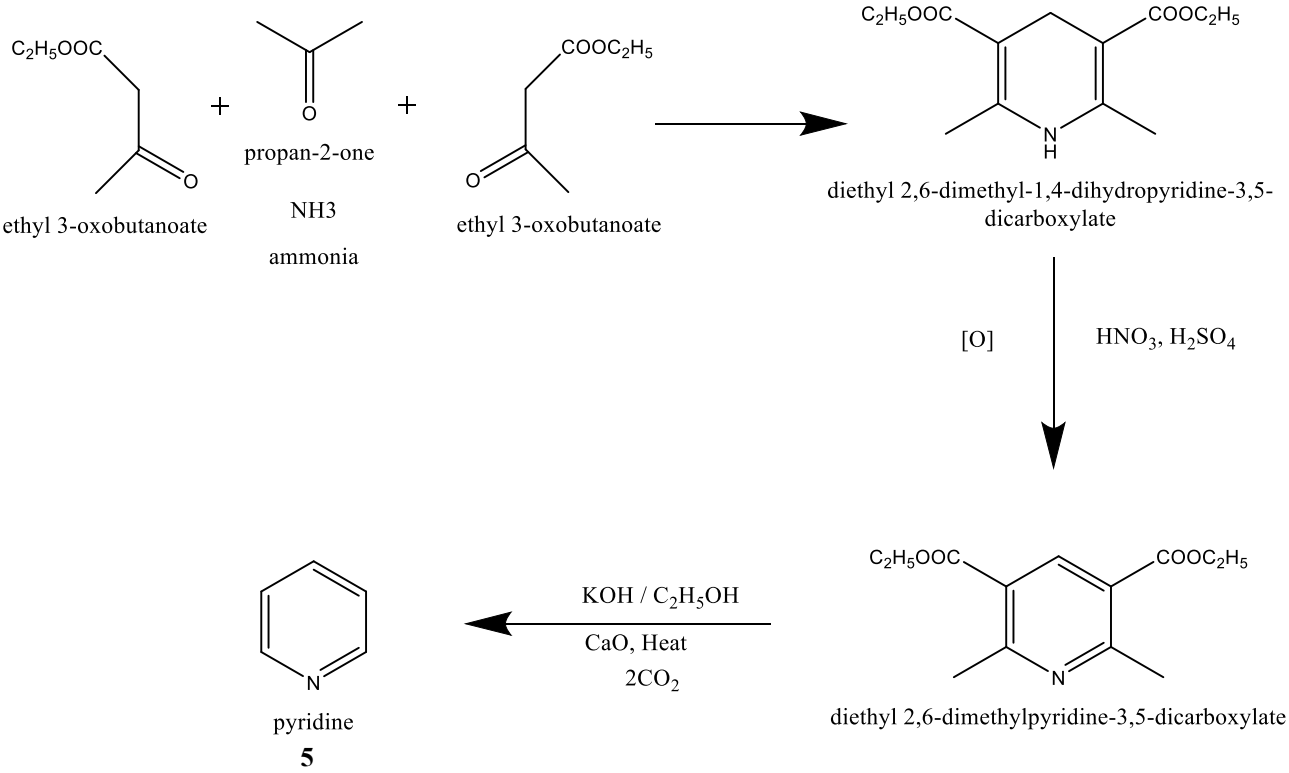


Acetylene hydrogen cyanide Acetylene pyridine

4

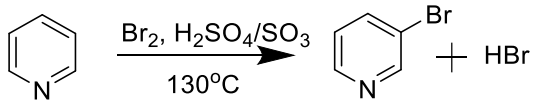
2. Hantzsch Synthesis of Pyridine

The synthesis of Pyridine can be achieved through various methods. But one of the most Common & well-established approaches is the Hantzsch Dihydropyridine synthesis. This method involves the condensation of beta-ketoester (such as Ethyl acetoacetate) & ammonia and an aldehyde (formaldehyde).[14, 15]

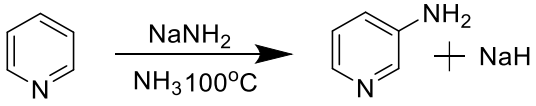


CHEMICAL REACTIONS OF PYRIDINE

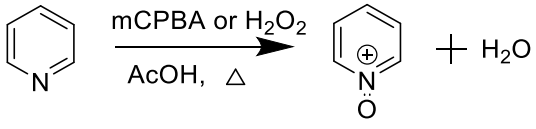
1. Electrophilic Aromatic Substitution (EAS)[16]



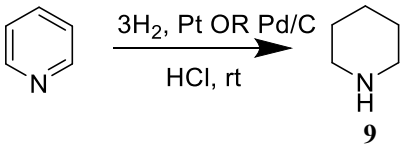
2. Nucleophilic Aromatic Substitution (The Chichibabin Reaction)[17]



3. N-Oxidation (Activation of the Ring)[18]



4. Reduction Reactions[19]

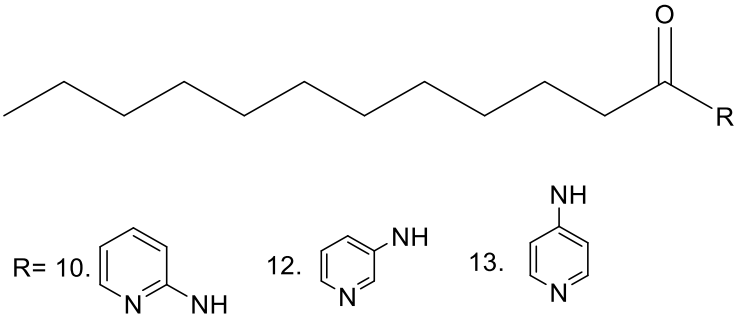


BIOLOGICAL ACTIVITY

1. Antimicrobial Activity of Pyridine Derivatives

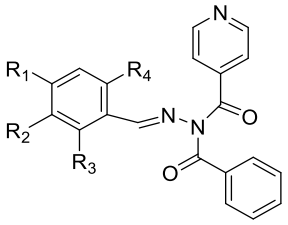
Sarova et al. have synthesized three dodecanoic acid derivatives **10** − **13** with yields of 59–61%, starting from dodecanoic acid in two steps, chlorination with thionyl chloride and reaction with the corresponding

aminopyridine. All compounds possessed good antibacterial activity against *B. subtilis*, *S. aureus* and *E. coli* and antifungal activity against *A. niger* and *C. albicans*. [20]



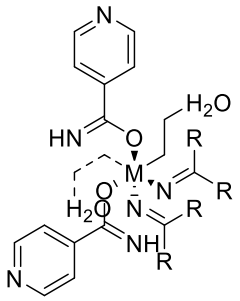
10-13

Judge et al. have synthesized a series of isonicotinic acid hydrazide derivatives by benzoilation of (*E*)-N'-benzylideneisonicotinohydrazide compounds and found that derivative **14** were the most active antimicrobial agents against the tested strains *S. aureus*, *B. subtilis*, *E. coli*, *C. albicans*, and *A. niger*, with MIC between 2.18−3.08 μM mL^{-1}. [21]



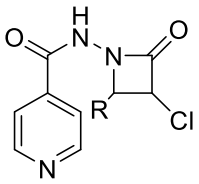
14

Bottari et al. have synthesized pyridine-derived Cu (II) and Ni (II) metal complex **15** and exploited them in antibacterial activity study. The anti-bacterial activity was evaluated against Myco-bacterium tuberculosis H37Rv.[22]



15

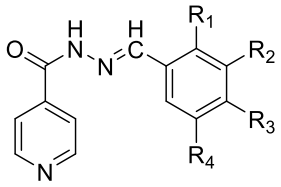
Elumalai et al. have reported a novel pyridine-derived compound **16** which showed the anti-microbial against gram-positive bacteria (B. subtilis), gram-negative bacteria (E. coli), M. tuberculosis (H37Rv) and *M. tuberculosis* (CIP). [23]



16

2. Antibacterial Activity of Pyridine Derivatives

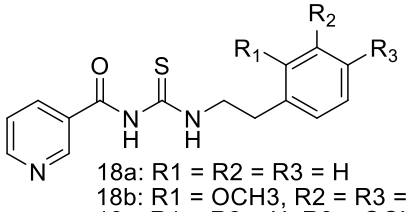
Narang et al. have synthesized nicotinic acid benzylidene hydrazide derivatives and evaluated their antimicrobial activity. The antimicrobial screening results indicated that compounds with nitro **(17d, 17e, and 17f)** and dimethoxy **(17g)** substituents have better antibacterial activity against *B 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. [24]



17d: R1 = NO2, R2 = R3 = R4 = H
17e: R2 = NO2, R1 = R3 = R4 = H
17f: R3 = NO2, R1 = R2 = R4 = H
17g: R1 = R4 = OCH3, R2 = R3 = H

17(d-g)

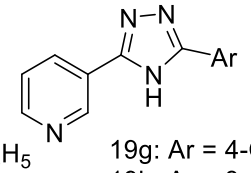
Ozgeris et al. have synthesized nicotinoyl compounds **18 (a-e)** and evaluated their antibacterial activity. At a MIC value of 31.25–62.5 µ g/mL, all these compounds exhibit excellent antibacterial activity against various bacterial strains such as *S. aureus, E. coli, E. faecalis, P. aeruginosa* and *A. baumannii.* [25]



18a: R1 = R2 = R3 = H
18b: R1 = OCH3, R2 = R3 = H
18c: R1 = R2 = H, R3 = OCH3
18d: R1 = R2 = H, R3 = F
18e: R1 = H, R2 = R3 = OCH3

18 (a-e)

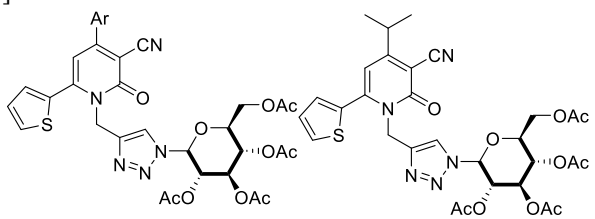
Panda et al. have synthesized pyridine-triazoles, **19 (a-k)**, and evaluated their antimicrobial activity. Compounds **19 (i-k)** showed excellent antimicrobial activity, substituted with trimethoxy phenyl, furanyl, and thiophenyl. In addition, compounds **19b, 19d, 19g and 19h** also showed good antimicrobial activity to a similar extent as that of the standard Miconazole and Ciprofloxacin. [26]



19a: Ar = C_6H_5
19b: Ar = 4-FC_6H_4
19c: Ar = 4-ClC_6H_4
19d: Ar = 4-BrC_6H_4
19e: Ar = 4-OHC_6H_4
19f: Ar = 4-$CH_3C_6H_4$
19g: Ar = 4-$OCH3C_6H_4$
19h: Ar = 3,4-$(OCH3)_2C_6H_3$
19i: Ar = 3,4-$(OCH_3)_2C_6H_3$
19j: Ar = 4-Furanyl
19k: Ar = 2-Thiopheyl

19 (a-k)

Morsy et al. have synthesized functionalized nicotinonitriles based 1,2,3-triazole nucleosides a, b and c. Compounds **20a, 20b and 20c** exhibit good in vitro antibacterial activity against *S. aureus* (ATCC 6538), *P. aeruginosa* (ATCC 9027), *M. luteus* (ATCC 10240), *E. coli* (ATCC 10536), *A. Niger* (ATCC 16404), and *C. albicans* (ATCC 10231). [27]

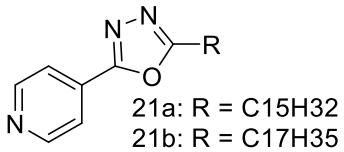


20a: Ar = 4-ClC_6H_4
20b: AR = 3-methylthiophen-2-yl

20 (a-b) **20c**

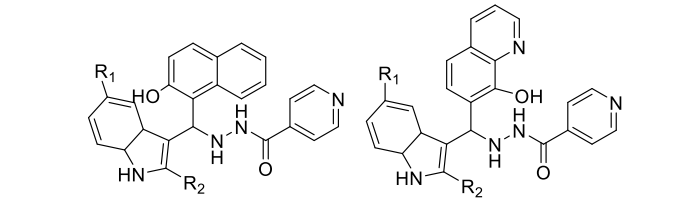
3. Antitubercular Activity of Pyridine Derivatives

Navarrete-Vázquez et al. have synthesized 4-(5-substituted-1,3,4-oxadiazol-2-yl) pyridines **21a** and **21b** from INH and acid chlorides, Compound **21a** showed 10 and 20 times more potency than INH and STR, respectively, against the INH-resistant *M. tuberculosis* CIBIN 112 strain. Moreover, this compound was 27 times more active than ETH. Compound **21b** showed the same behaviour as **21a** against this strain. [28]



21 (a-b)

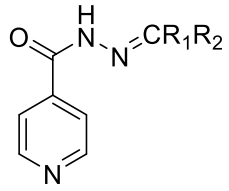
Rathod et al. have synthesized a series of INH compounds **22a**–**22d** and **23a**–**23d** using multicomponent reactions in good yields (80–94%), Electron-withdrawing groups were reported to increase the anti-TB activity. [29]



a: R1 = Cl, R2 = Ph, b: R1 = CH3, R2 = Ph, c: R1 = H, R2 = Ph, d: R1 = R2 = H

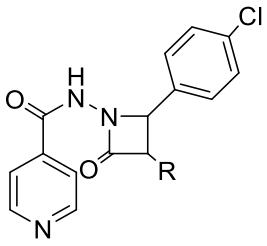
22 (a-d) **23 (a-d)**

Hearn et al. have reported the lipophilic adaptations of the structurally modified frontline antitubercular pyridine-derived isonicotinic acid hydrazide drug **24** 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. [30]



24

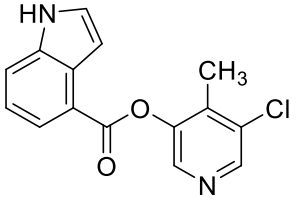
Thomass et al. have designed a series of amino azetidinones from respective azetidin-2-ones by in silico methods. In turn, the azetidin-2-ones were prepared from the reaction of isoniazid Schiff bases with chloroacetyl chloride. Using the Alamar blue assay method, it was found that the synthesized compounds have significant antitubercular activity. [31]



25

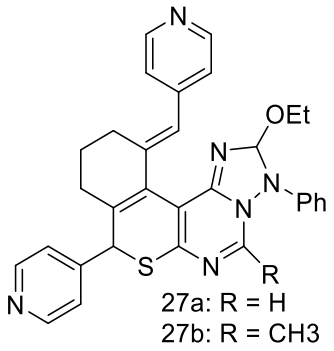
4. Antiviral Activity of Pyridine Compounds

Ghosh et al. have reported synthesis of 5-chloro-4-methylpyridin-3-yl-1*H*-indole- 4 carboxylate **26** from 5-chloro-4-methylpyridin-3-ol and 1H-indole-4-carboxylic acid in the presence of EDC (1-ethyl-3-carbodiimide hydrochloride) and DMAP (4-dimethyl aminopyridine) using dichloromethane as solvent. Compound **26** exhibited potent antiviral activity. [32]



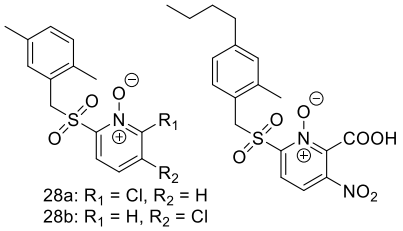
26

Abu-Hashem et al. have reported the synthesis of compounds **27a**. The data revealed that isothiochromeno-triazolo pyrimidines **27a** and **27b** have promising in vitro antiviral activity against herpes simplex virus-1 (HSV-1) and human immunodeficiency virus-1 (HIV-1). [33]



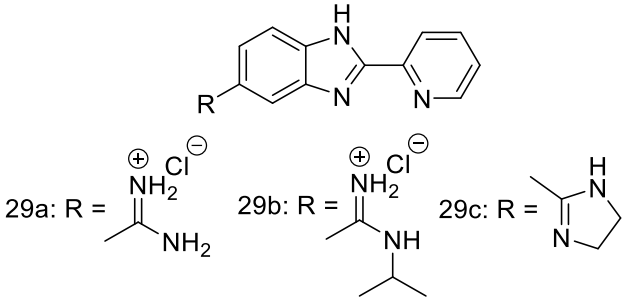
27(a-b)

Stevens et al. have synthesized pyridine N-oxide derivatives **28a, 28b,** and **28c**, the activity of these compounds was evaluated against SARS and feline coronavirus. Interestingly it was found that compounds **28a** and **28b** have potential activity against SARS-CoV and feline coronavirus strain. [34]



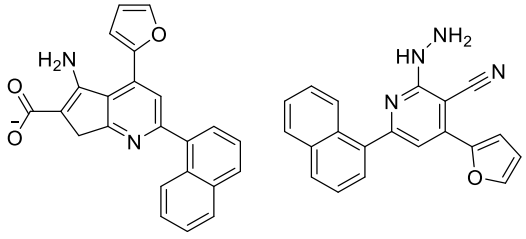
28 (a-b) **28c**

Starčević et al. have synthesized 2-substituted-5-amidino-benzimidazoles, **29(a-c)** and evaluated antiviral activity. All three compounds showed outstanding antiviral activity against Coxsackie virus B5 and echovirus 7 with an EC_{50} value of 0.33–56.7Mm. [35]



29 (a-c)

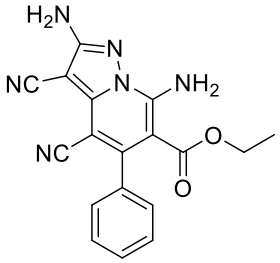
Salem et al. have synthesized compounds **30a** and **30b** and evaluated their antiviral activity against adenovirus type 7 and rotavirus Wa strain.. Compound **30b** showed a 50 % and 53.3 % reduction with adenovirus type 7 and rotavirus Wa strain respectively. [36]



30a **30b**

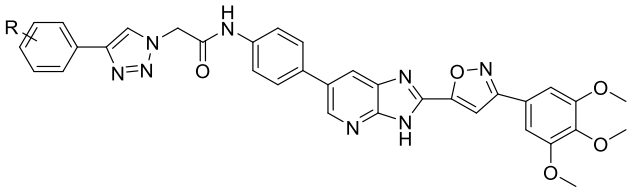
5. Anticancer activity of Pyridine Derivatives

Naik et al. have synthesized a series of substituted pyrazolo[1,5-a] pyridine derivatives using a one-pot DMAP-catalysed method. The compounds showed promising anticancer activity, compound **31** was found to be more active in single high dose preliminary test and progressed to the five high dose assays. [37]



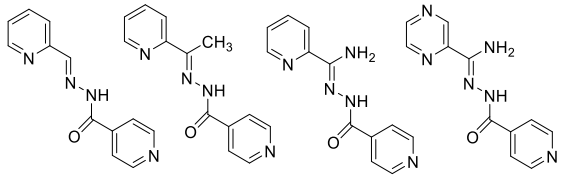
31

Murthy et al. have synthesized a series of pyridine-derived compounds **32(a-j)** containing imidazole and triazole moieties and evaluated the in vitro anticancer activities against HepG2 and A549 carcinoma cells. [38]



32(a-j)

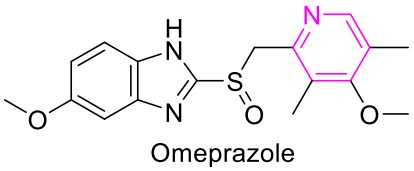
Firmino et al. have reported the cytotoxicity of some pyridine-derived compounds **33a, 33b, 33c,** and **33d** and their copper complexes. The anti-cancer activity of these compounds was carried out against M. tuberculosis (H37Rv) strain and the human ovarian (OVCAR-8), glioblastoma multiforme (SF-295) and colon adenocarcinoma (HCT-116) cancer cells. [39]



33a **33b** **33c** **33d**

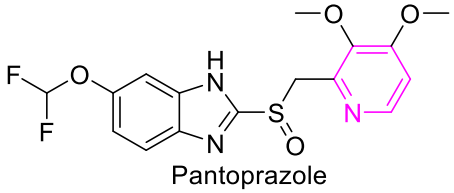
Pharmacologically active marketed drugs containing pyridine ring

1. **Gastrointestinal Drugs (Proton Pump Inhibitors)**



Omeprazole

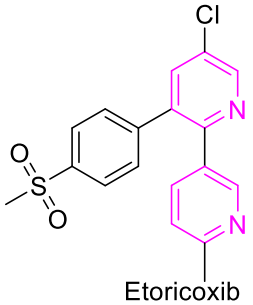
34



Pantoprazole

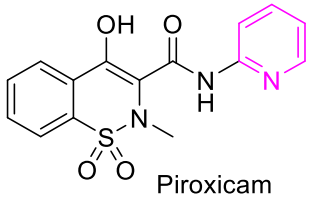
35

2. **Anti-inflammatory & Analgesic Drugs (NSAIDs)**



Etoricoxib

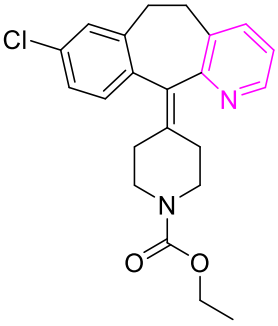
36



Piroxicam

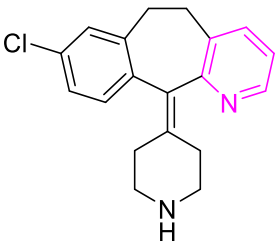
37

3. **Antihistamines (Allergy Medications)**



Loratadine

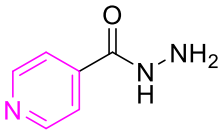
38



Desloratadine

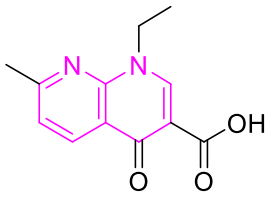
39

4. **Antimicrobial & Antibacterial Drugs**



Isoniazid

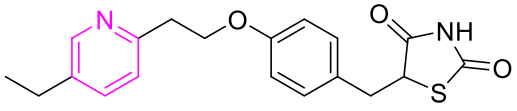
40



Nalidixic Acid

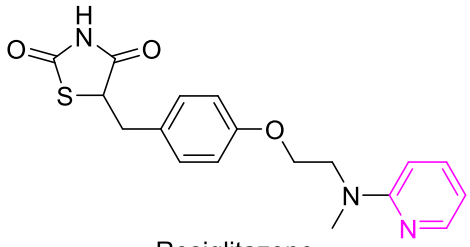
41

5. **Metabolic & Cardiovascular Drugs**



Pioglitazone

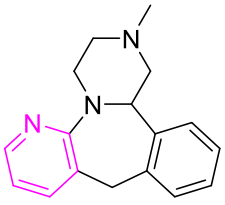
42



Rosiglitazone

43

6. **Neurological & Psychiatric Drugs**



Mirtazapine

44

CONCLUSION:

Pyridine derivatives are an important class of heterocyclic compounds widely used in organic and medicinal chemistry. Over the years, these compounds have attracted significant attention because of their broad range of biological and pharmacological activities. Different pyridine-based derivatives have shown promising antimicrobial, antibacterial, antitubercular, antiviral, and anticancer properties. Many researchers have reported that slight structural modifications in the pyridine ring can improve their biological activity and effectiveness against different diseases. The presence of pyridine in several clinically useful drugs further highlights its importance in drug discovery and development. From the literature reviewed, it can be concluded that pyridine derivatives have great potential for the development of new and more effective therapeutic agents, especially for the treatment of infectious diseases and drug-resistant tuberculosis.

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