Benha University

Chemistry Department

Applied Chemistry Division

GRADUATION PROJECT

Pyridine and its derivatives in life applications

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Contents

Abstract:

In the context of the new life-threatening COVID-19 pandemic caused by the SARS-CoV-2 virus, finding new antiviral and antimicrobial compounds is a priority in current research. Pyridine is a privileged nucleus among heterocycles; its compounds have been noted for their therapeutic properties, such as antimicrobial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory, antioxidant, anti-Alzheimer's, anti-ulcer or antidiabetic.

It is known that a pyridine compound, which also contains a heterocycle, has improved therapeutic properties. The singular presence of the pyridine nucleus, or its one together with one or more heterocycles, as well as a simple hydrocarbon linker, or grafted with organic groups, gives the key molecule a certain geometry, which determines an interaction with a specific protein, and defines the antimicrobial , antiviral selectivity, antitubercular ,antimalarial ,anticancer and antiinflammatory for the target molecule. Moreover, an important role of pyridine in medicinal chemistry is to improve water solubility due to its poor basicity.

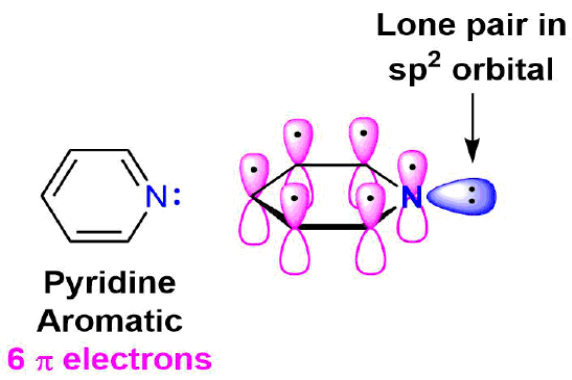
In this article, we aim to review the methods of synthesis of pyridine compounds, their antimicrobial and antiviral activities, the correlation of pharmaceutical properties with various groups present in molecules as well as the binding mode from Molecular Docking Studies

Introductioon :

Structure of Pyridine

Pyridine is a basic heterocyclic organic compound with the chemical formula C5H5N.

Pyridine has a conjugated system of six π-electrons exactly as benzene has, that are delocalized over the heterocyclic ring. The molecule is planar in nature and follows Hückel criteria for aromaticity, Pyridine has planer , hexagonal ring.



Its structure was determined by Wilhelm Körner in 1869 and James Dewar in 1871, independently.

It was suggested that the structure of pyridine might be analogous to quinoline and naphthalene.

It was concluded that pyridine has been derived from benzene and its structure might be obtained by replacing a CH moiety with a nitrogen atom.

Basic Properties

This simplest and most common compound is water-miscible, flammable, and colorless to yellow liquid (bp 115.5°C and mp -41.6°C).

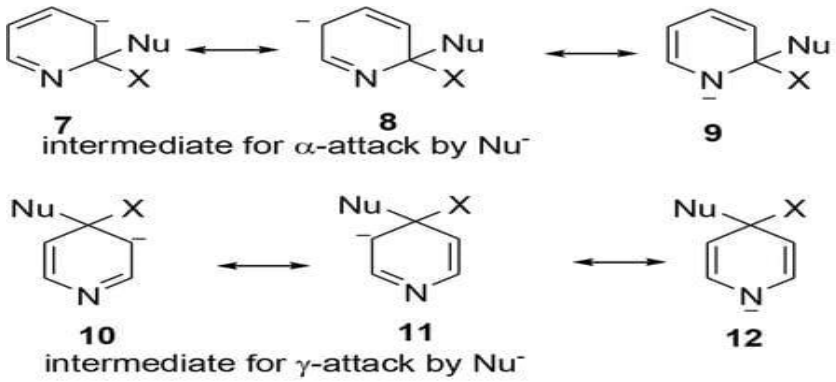
Due to water miscibility, it is used to dissolve other substances. However, pyridine bears an unpleasant/foul smell and some hazardous properties.

Pyridine is more polar than benzene due to the nitrogen atom.

Chemical Properties

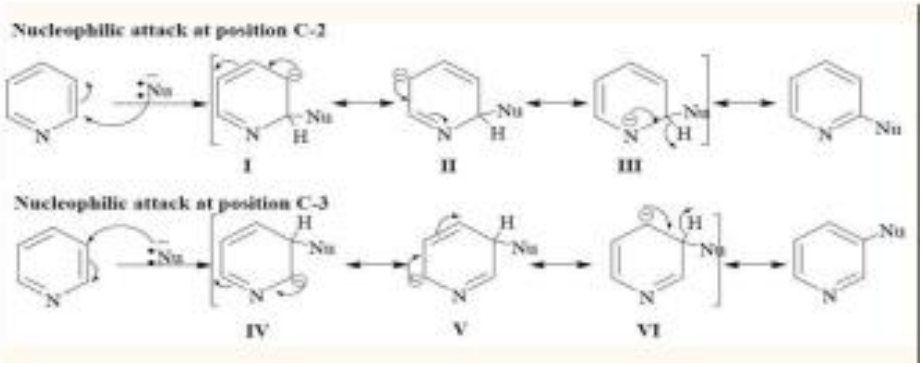
Pyridine is a weak base (pKa of conjugate acid ~5.2) because the lone pair on nitrogen is available for protonation.

It Less reactive than benzene toward electrophilic aromatic substitution (EAS), More reactive toward nucleophilic substitution, especially at the 2- and 4-positions.



Generally, electrophilic substitutions on pyridine either do not proceed or if it does, it proceeds only partially. However, the hetero-aromatic character of pyridine can be activated by electron donating functionalization. Pyridine does not undergo common alkylation's and or acylation's reactions such as Friedel Crafts alkylation or acylation reaction, because these only lead to addition at the nitrogen atom. Substitutions usually occur at the 3-positions (Ortho, Meta and Para).

Direct nitration of pyridine requires very harsh conditions and has very low yield. However, for our purposes here, survive it to note that in an attempt to nitrate pyridine, the first thing that will happen is that the strong acid, and thus, generate the pyridinium cation. The ring in the pyridinium cation is even more deactivated than the pyridine ring because of the full unit of positive charge on the nitrogen; but again, if we look at the possible resonance structures, we find that, meta-attack/substitution will be preferred. In this case the ring is so



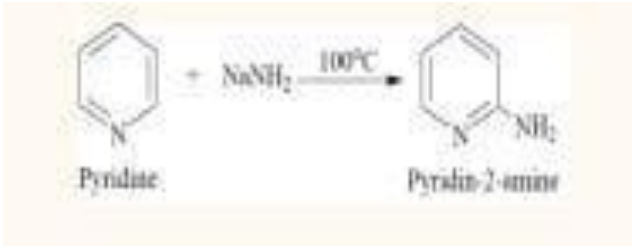
deactivated that extremely vigorous conditions must be used to nitrate the ring.

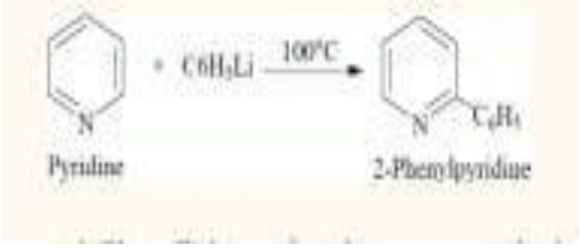
As we have discussed in the electrophilic reaction that pyridine generally deactivated the aromatic ring towards electrophilic substitution reaction. The deactivation of the aromatic rings towards electrophilic substitution resulted due to the electron-withdrawing nature of the nitrogen atoms [6]. Due to such deactivation, Pyridine also gives nucleophilic substitution reaction.

Nucleophilic substitution in pyridine ring occurs at position C-2. Approach of the nucleophilic at position C-2 leads to the formation of three resonating structures (I, II and III).

Similarly, the approach of nucleophilic at position C-3 also leads to the formation of three resonating structures (IV,V and VI).

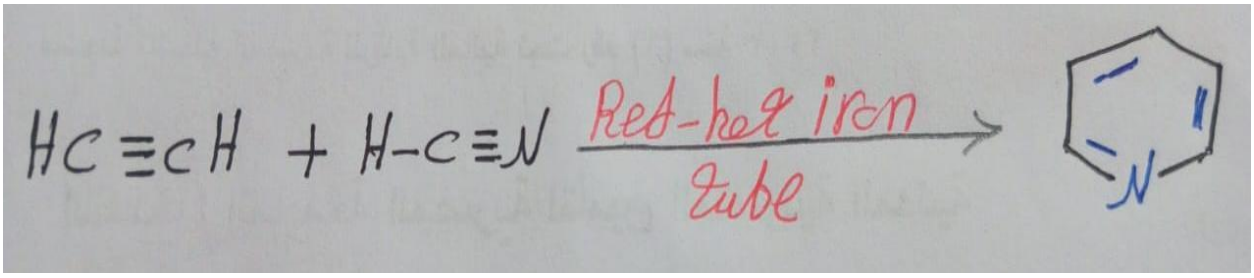
The resonating structures for intermediate resulting from the attack of the nucleophile at position C-2 are more stable than those of position C-3 since more electronegative nitrogen atoms hold a -ve charge in one of the resonating structures (III) obtained from the attack of the nucleophile at position C-2. Hence, the nucleophilic substitution in pyridine at position C-2 is always favored.





Industrial Preparation of Pyridine

In the year 1876, William Ramsay synthesized this compound by combining acetylene and hydrogen cyanide, a red-hot iron-tube furnace was used to carry out the reaction. It was the ever first synthesis of a hetero-aromatic compound. Pyridine became an interesting target in 1930.



From Acetaldehyde, Ammonia, and Formaldehyde

Process:

Mixture passed over a catalyst (e.g., aluminum oxide) at high temperatures (~400–500°C).

Reactants:

3 molecules of acetaldehyde (CH_3CHO)

1 molecule of ammonia (NH_3)

Reaction Conditions

Temperature: ~400–500°C

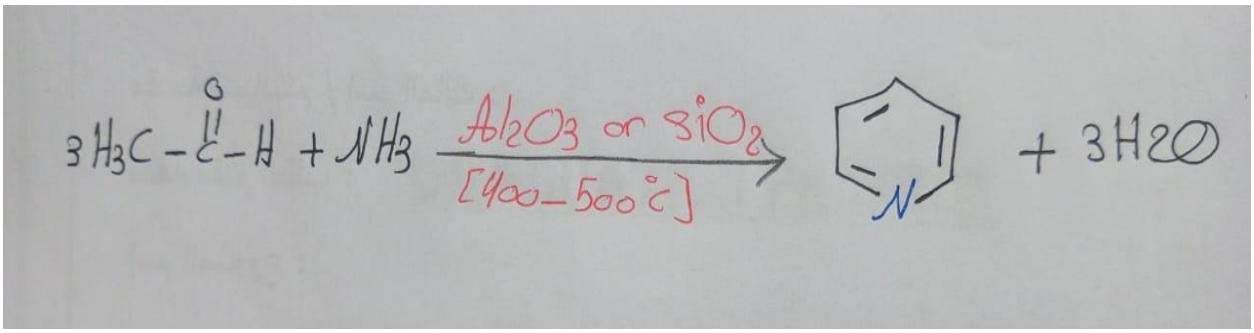
Catalyst: Alumina (Al_2O_3), silica (SiO_2), or other metal oxides

Phase: Gas phase continuous process

Products:

1 molecule of pyridine (C_5H_5N)

3 molecules of water (H_2O)



From Petroleum Derivatives (Modern Industrial Method), Pyridine and its derivatives can also be extracted as by-products from coal tar.

However, today, synthesis from small molecules (acetaldehyde + ammonia) using heterogeneous catalysts is the main commercial process.

Importance of pyridine

Pyridine nuclei are found in many natural products, including vitamins, alkaloids, coenzymes, and many drugs and pesticides .

Pyridine and its derivatives are polar and ionizable aromatic compounds that improve their solubility and bioavailability parameters .

Pyridine and its derivatives are valuable heterocyclic compounds that play a vital role in various biomedical applications.

Synthesis of different derivatives of pyridine with their applications :-

Anti-Microbial Compounds:-

Sarova et al (1). synthesized three dodecanoic acid derivatives 1–3 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 antifungal activity

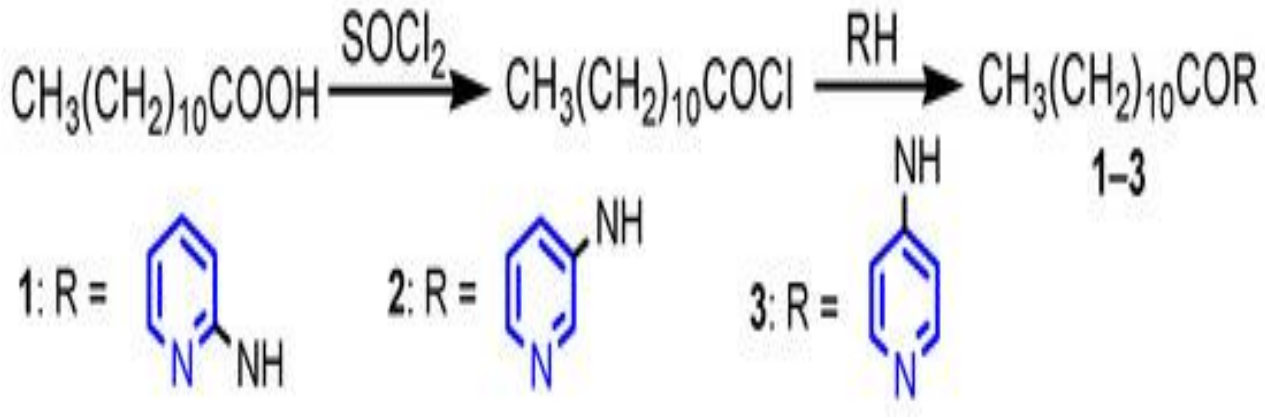


fig 1. Synthesis of dodecanoic acid pyridines 1–3

Furdui et al (2). reported efficient synthesis of symmetrical diquaternary salts by alkylation of 4-[2-(pyridin-4-yl) ethyl] pyridine or 4,4'-bipyridine, with various bromo- or chloro-acetophenone analogues and investigated

their antimicrobial activity against nine different microorganisms: *B. subtilis*, *B. cereus*, *S. lutea*, *R. glutinis*, *C. utilis*, *S. cerevisiae* and *P. roqueforti*.

Compounds 42a–42d, 43a and 43d show efficient inhibitory properties at least against one bacterial strain.

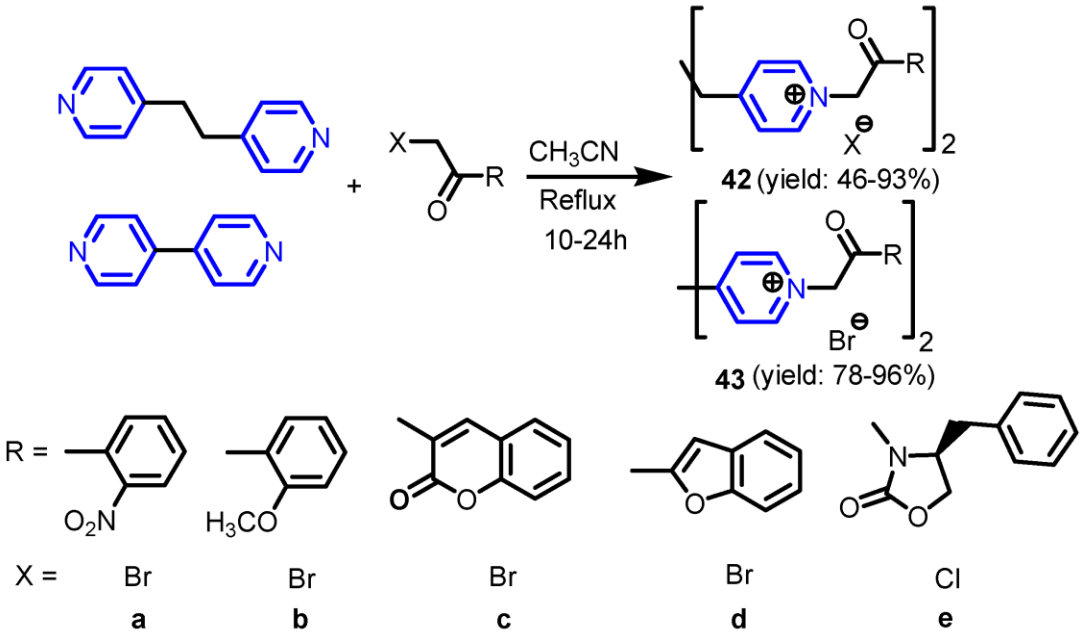


Fig 2 . Synthesis of bis-pyridinium quaternary ammonium salts

Brycki et al(3). performed a Menshutkin reaction between 4-chloromethylpyridine and the N,N-dimethylalkylamines containing 8, 10, 12, 14, 16, 18 carbon atoms in an alkyl chain, respectively in acetonitrile to obtain compounds **51**–**56** in good yields at room temperature (fig 3).

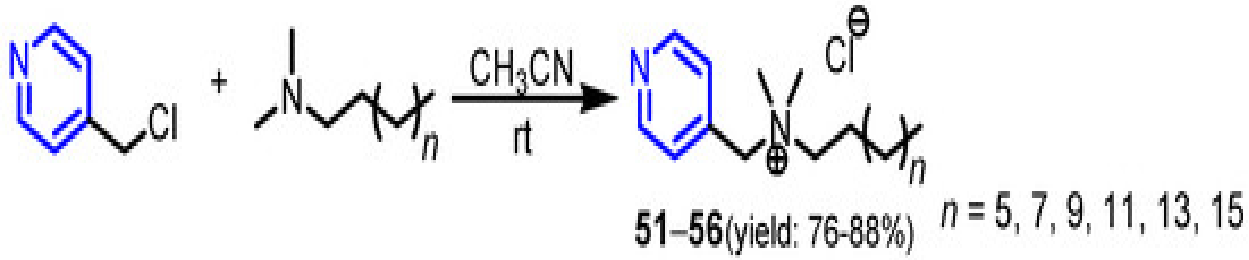


Fig 3. Synthesis of pyridine salts **51**–**56**.

Tamilvendan et al. (**4**) synthesized pyrol-pyridine bases:

(1-((pyridin-2-ylamino)methyl)pyrrolidine-2,5-dione **74**

1-(phenyl(pyridin-2-yl amino)methyl) pyrrolidine-2,5-dione **75** using a classical Mannich reaction between succinimide, aniline, and formaldehyde or benzaldehyde (fig 4) in good yields (78–80%).

Both compounds showed moderate antimicrobial activity against the antibacterial panel (*Salmonella typhi*) and antifungal agents (*Aspergillus oryzae).*

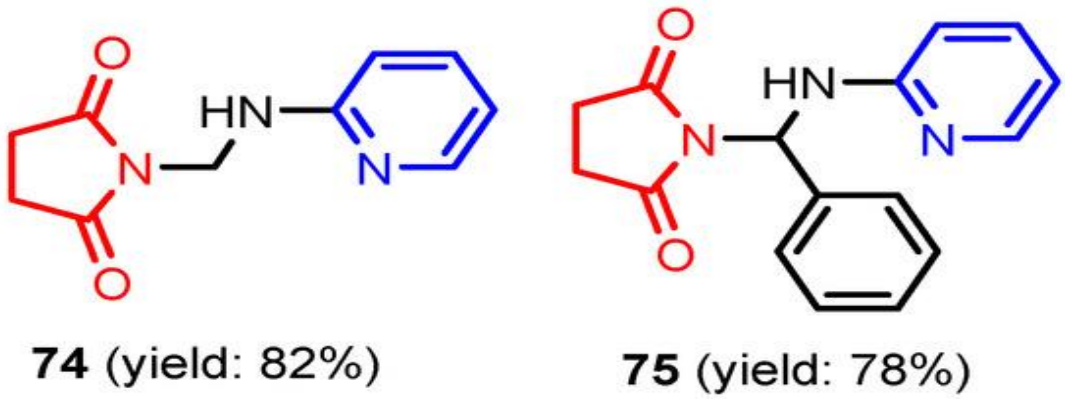


Figure 4. Structure of Mannich pyrol-pyridine bases **74** and **75**

Murty (5) synthesized 1,3,4-oxadiazoles–pyridines 117a–117c through an oxidative C–O coupling by direct C–H bond activation of N-aroyl-N-arylidinehydrazines 116a–116c using a catalytic quantity of CuO nanoparticles (fig 5).

Compound 117a showed broad-spectrum antibacterial activity for all tested strains, and compounds 117a and 117b exerted antifungal activity better than standard drug, Cycloheximide.

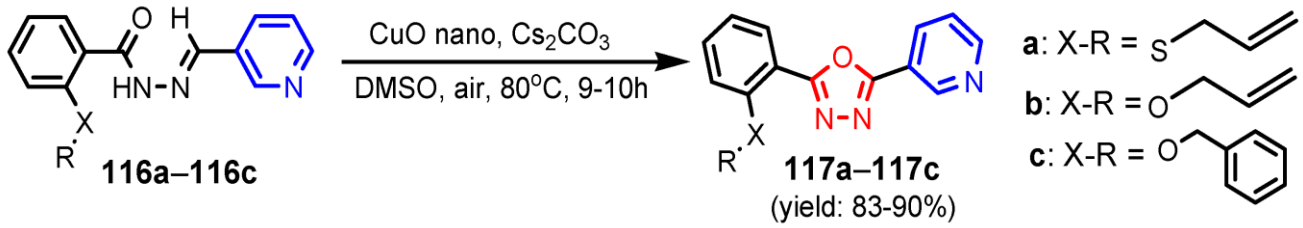


Fig 5. Synthesis of 1,3,4-oxadiazoles–pyridines **117a–117c**.

Krishna [6], synthesized compound **120** in two steps: alkylation of 4-hydroxy-2H-chromen-2-one **118** to give ester **119**, which by condensation reaction with (Z)-N'-hydroxy isonicotinimidamide under reflux temperature for 24 h, gave :-

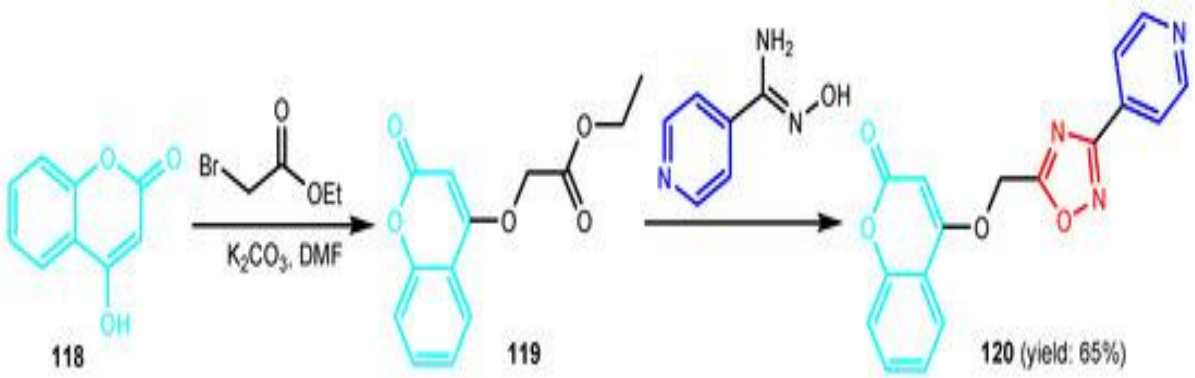


Fig 6 Synthesis of 4-[(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)methoxy]-coumarin.

Compounds **121** and **122** were synthesized by similar reactions (fig6) and showed good antibacterial activity against *S. aureus* and *E. coli*, and *pyridines* **120**–**122** present antifungal activity than that of standard drug, Clotrimazole

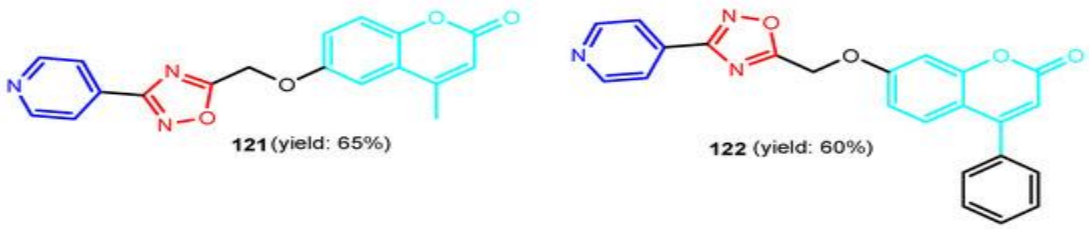


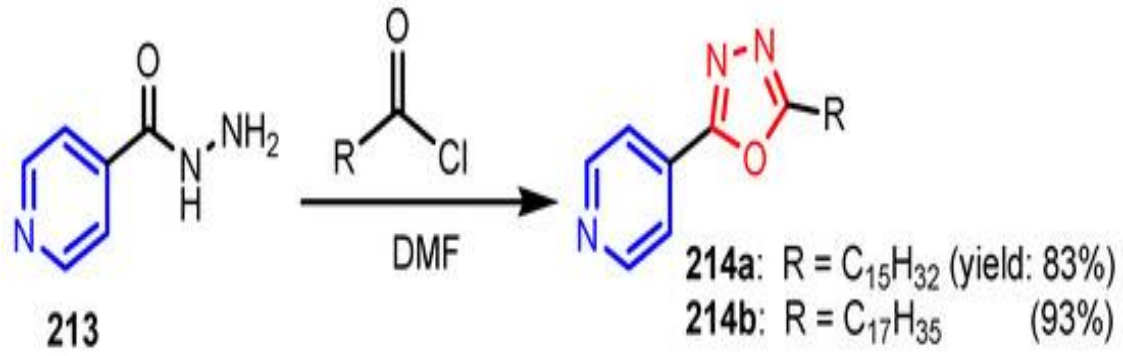
Fig7. Structure of 1,2,4-oxadiazol-coumarin-pyridines **121** and **122**.

Anti-Tubercular Pyridine Compounds :-

Tuberculosis (TB) remains a major threat to global public health, with at least 10 million new cases and 1.2 million deaths in 2019. The high incidence and mortality rates of TB can be attributed to the capacity of its etiological agent, intracellular bacterium Mycobacterium tuberculosis , to adapt to and survive in the aggressive physiological environment within the host . The need for new tuberculostatic agents arises due to bacterial resistance.

Navarrete-Vázquez [7] synthesized4-(5-substituted-1,3,4-oxadiazol-2-yl) pyridines 214a and 214b from INH (Isoniazid) and acid chlorides (fig 8),

Compound 214a showed 10 and 20 times more potency than INH, respectively, against the INH- resistant , this compound was 27 times more active than ETH(Ethambutol). Compound 214b showed the same



behavior as 214a against this strain.

Fig 8. Synthesis of (1,3,4-oxadiazol-2-yl) pyridines **214a**–**214b**.

Anti-Viral Pyridine Compounds:-

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 for treating a variety of deadly viral diseases.

The majority of antiviral medications aim to stop the development of certain viruses.

Starčević [8] reported the synthesis of 2-substituted-5-amidino-benzimidazoles 230a–230c from the reaction of 1,2-phenylenediamine 228 and picolinaldehyde 229. All compounds possessed excellent antiviral activity against coxsackievirus B5 and echovirus 7 (fig 9).

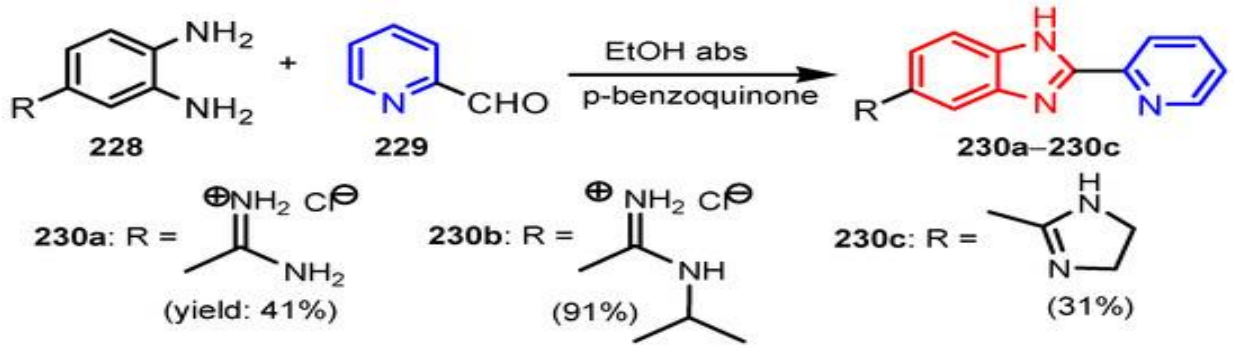


Fig 9. Synthesis of pyridine compounds **230a**–**230c**

Pyridine derivatives are a great class of chemical molecules to work with for creating new and potent antiviral medications. Given the wide range of physiological actions exhibited by pyridine-derived compounds, they are essential in the field of medicinal chemistry.

Balzarini et al. synthesized pyridine N-oxide derivatives **a**, **b**, and **c** (Fig. 10) 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.

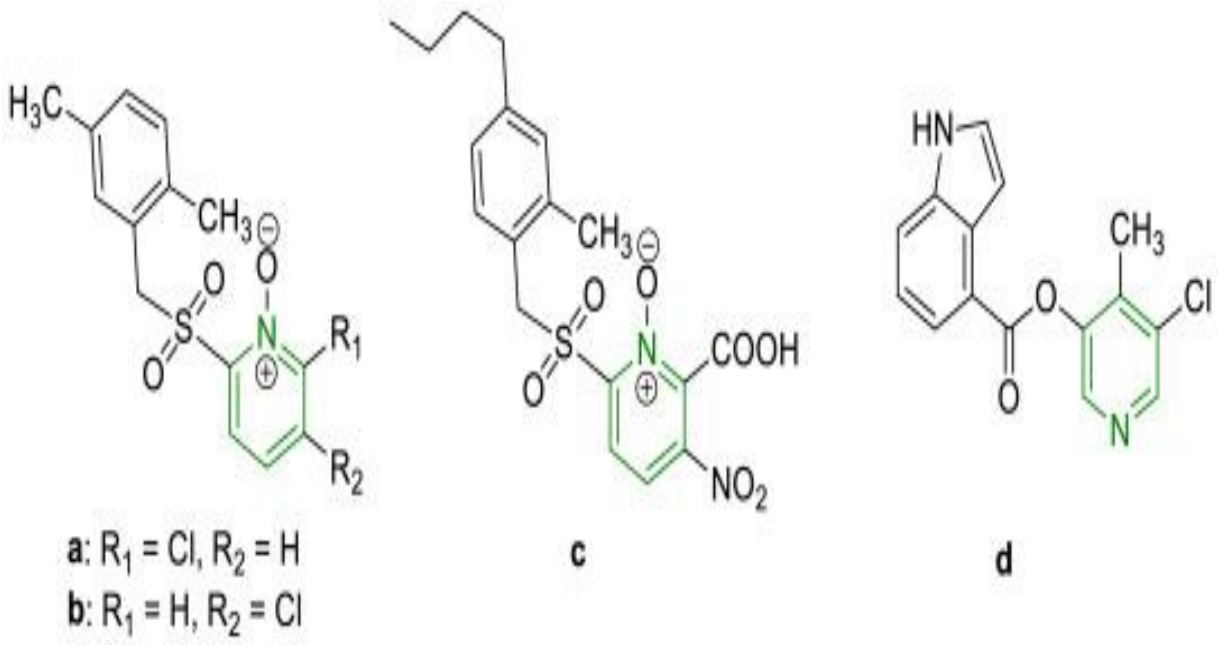


Fig10. Structures of compounds **a**, **b**,**c** and 5-chloro-4-methylpyridin-3-yl-1H-indole- 4-carboxylate, **d**.

Anti-Malarial Agents :-

Some compounds 35 and 36 of pyridine quinoline as hybrid molecules were tasted for their anti-malarial activities , the results showed that these molecules are poor anti-malarial activity. These compounds give a clue that they can be used as templates for designing new anti-malarial drugs and their activities can be improved. These molecules also showed haem polymerization inhibition (HPIA) activities .

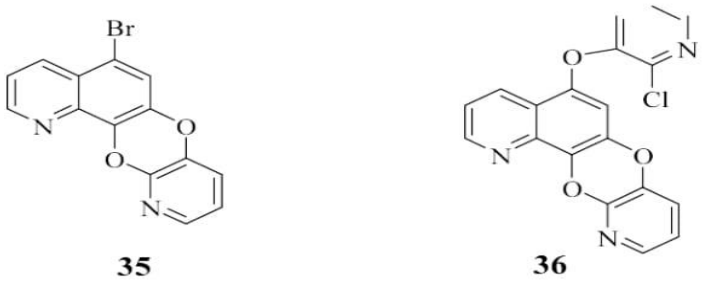


Fig 10. Macromolecular structures containing pyridine

Anti-Bacterial Activity :-

synthesized nicotinic acid benzylidene hydrazide derivatives and evaluated their antimicrobial activity. The antimicrobial screening results indicated that compounds with nitro (**d**, **e,** and **f**) and dimethoxy (**g**) substituents have better antibacterial activity against *B subtilis, S. aureus*, *E coli*,). Some of these have antimicrobial activity comparable to that of the fluconazole.

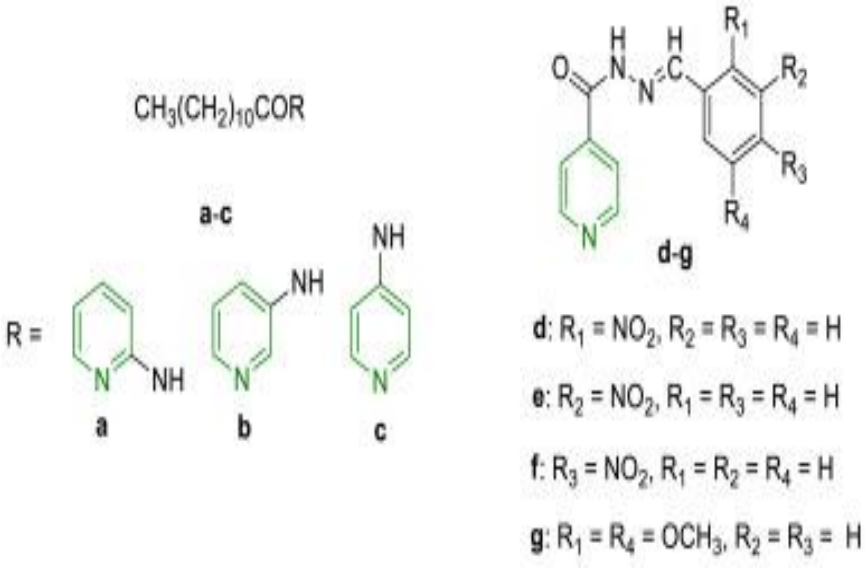


Fig. **11**. Structure of dodecanoic acid pyridines **a**-**c**, and nicotinic acid benzylidene hydrazide derivatives, **d**, **e**, **f**, and **g**.

Anti-Cancer Activity :-

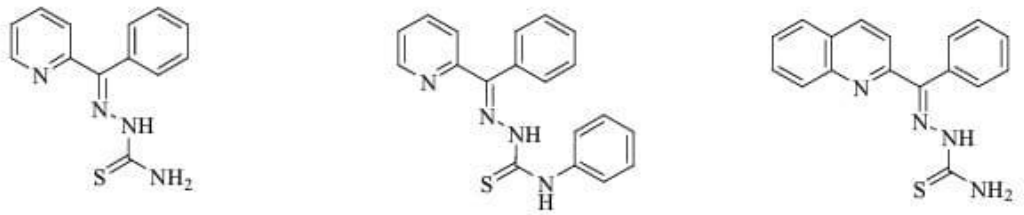
Thiosemicarbazone derivatives analogous to quinoline and isoquinolines which contain benzoylpyridine thiosemicarbazones are easy to synthesize.

When such compounds were checked for cytotoxic activities. They were found to exhibit moderate to good cytotoxicity against HuCCA-1, HepG2, A549 and MOLT-3 human cancer cells.

Benzoylpyridine thiosemicarbazones of type 32 and 33 and of of the quinoline analogues, 34 showed antimalarial activity in the range of mild to good.

It is suggested that some in these compounds particularly 33 is potential anticancer and antimalarial agents [9].

The pyridine derivatives containing substituents at 2- and (or) 6-position including heterocyclic substituents were obtained. The biological (anticancer) screening of these compounds show that they have good



32 33 34

Figure 12. *Thiosemicarbazones derived from pyridine as anticancer drugs.*

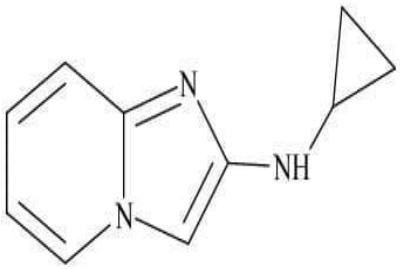
anticancer activity even better than those of references, 5-flurouracil (5-FU) and doxorubicin.

pyridine.[10] and their complexes with gallium(III) and iron(III) exhibit excellent anti-cancer activity against two human cancer cell line and their cytotoxicity mostly depend on central metal ions, gallium increase the cytotoxicity while iron decrease but ligand itself is more cytotoxic as compare to the central metal ions so metal ions interaction to the ligand decrease cytotoxicity .

Copper(II) complex of nitrogen containing heterocyclic thiosemicarabazone inhibite topo isomeraseII and proliferatin of breast cancer cell line.[11] 4-pyridyl anilinothioaazol (PAT) is used intreatment of renal cell carcinomas against Von Hippel Lindall (VHL) tumor activated and this will provide to a novel chemotype a target aproch for treatment of RCC.

Anti-Inflammatory Agents:-

A group of imidazo[1,2-a]pyridine derivatives have been synthesized similar to compound 37, the same exhibit antiinflammatory activities [12].



37

2-acetyl pyridine and 4-acetyl pyridine condence with some amide have excellent anti-inflammatory activity [13].

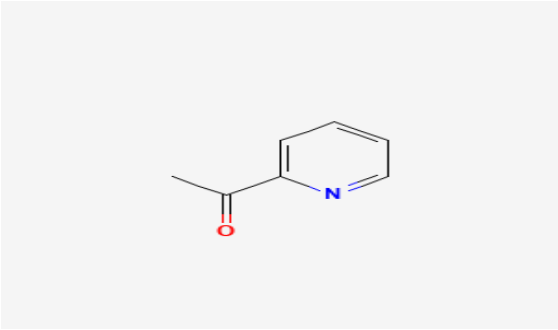


Fig 13. 2-acetyl pyridine

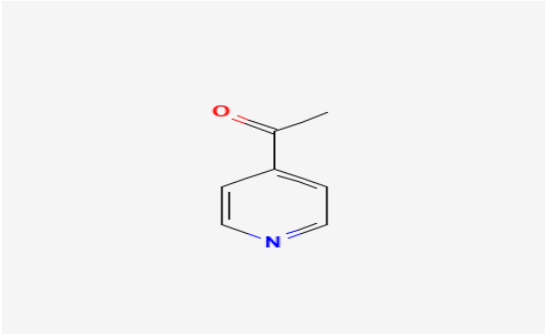


Fig 14.4-acetyl pyridine

Pyridine In Drug Design :-

Milrinone and amrinone are the two commercially available vasodilators [14]and contain both pyridine and dihydropyridine ring systems in their structures (Figure 15). In general, pyridine- and dihydropyridine-containing drugs are mostly used as anticancer, antioxidant, antihypertensive, antidiabetic, antimalarial, and anti-inflammatory agents and antiamebic agents.

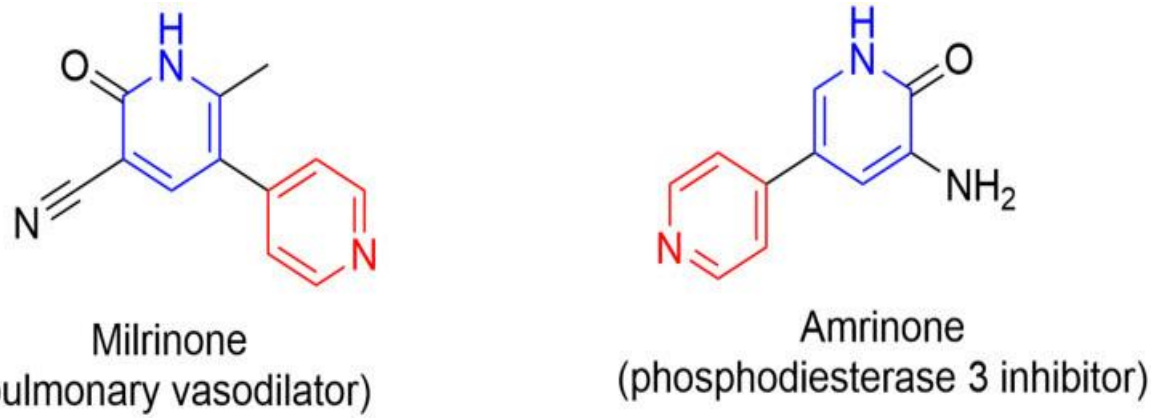


Figure 15. FDA-approved vasodilators containing both pyridine and dihydropyridine scaffolds.

There is a plethora of commercially available drugs in the market which contain pyridine rings, such as:-

abiraterone for prostate cancer, enpiroline for malaria, nicotinamide for pellagra, nikethamide as a respiratory stimulant, piroxicam for arthritis, isoniazid for tuberculosis, pyridostigmine for myasthenia gravis, tropicamide as an antimuscarinic, doxylamine for allergies, omeprazole

for ulcers, delavirdine as an antiviral against HIV/AIDS, enisamium iodide for influenza, and tacrine as an inhibitor of the AChE enzyme for Alzheimer's disease prevention (Figure 16).

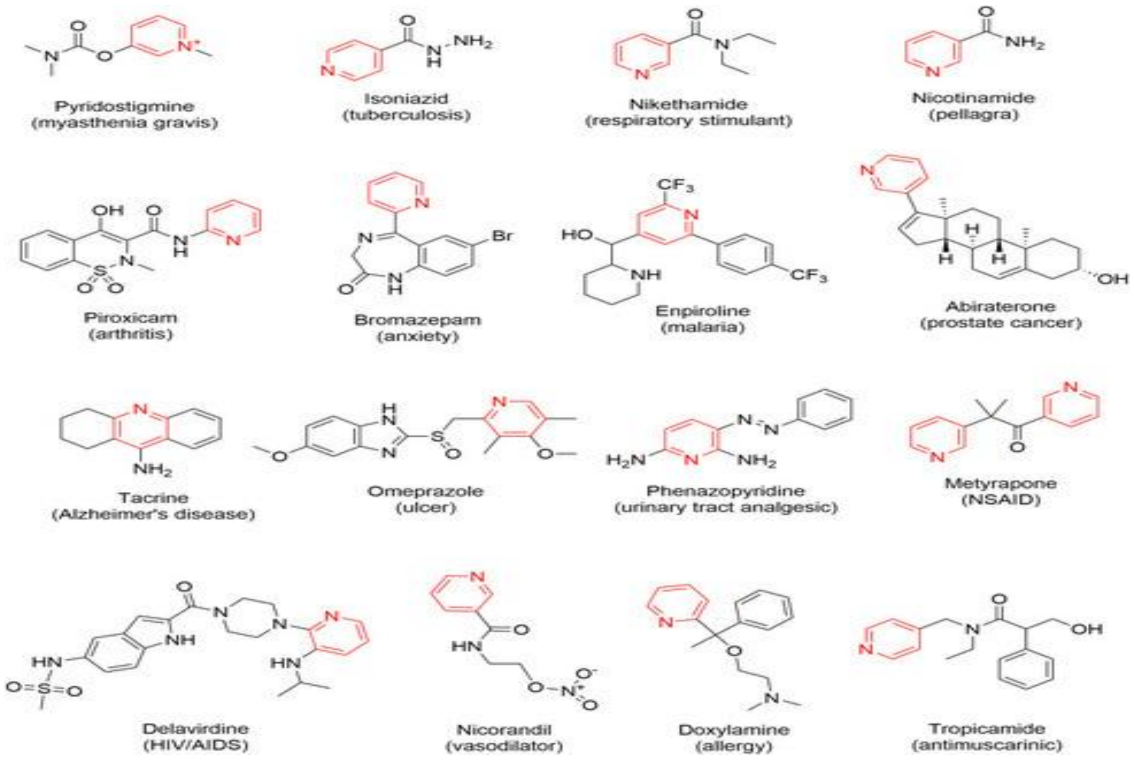


Figure 16. Some commercially available drugs containing the pyridine scaffold.

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