

REVIEW ARTICLE

Pyridine derivatives as preferable scaffolds for the process of discovering new drugs

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ABSTRACT

The pyridine ring is present in numerous significant plant compounds. It is used as a therapeutic to boost the solubility and bioavailability of less soluble chemicals since it is a polar and ionizable aromatic molecule. Chemical compounds derived from pyridine are highly sought-after in the pharmaceutical industry. An essential synthesis strategy in the search for novel medications is the fusion of the pyridine nucleus. Due to the compounds' powerful therapeutic characteristics, medicinal chemists have long been fascinated by the chemistry of pyridine and its derivatives, which inspires them to look for and make novel compounds with biological utility. There are significant ramifications for medical chemistry in the adaptability of pyridine and its derivatives as reactants and starting materials for structural changes. Pesticides and agricultural chemicals that heavily rely on pyridine derivatives include insecticides, fungicides, and herbicides; However, this page focuses on their medical applications. Pyridine derivatives are frequently used in the textile industry to create dyes. We present the most recent findings from 2010 onward, highlighting the growing significance of pyridine scaffolds in medicinal chemistry and the development of new drugs. Even though there are a lot of studies on pyridine derivatives, this chapter only has compounds with a clear pharmacophore.

Keywords: pyridine; medicinal chemistry; therapeutic property; discovery of new drugs

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1. Introduction

The ring atoms in the pyridine molecule are typically sp²-hybridised. Nitrogen shares a single pair of electrons that have no effect on the aromatic ring but are crucial for determining the chemical characteristics of pyridine. The global pyridine market is anticipated to rise from its 2021 value of over USD 1.1 billion to more than USD 2.4 billion by the end of 2028, with a predicted compound annual growth rate (CAGR) of 9.5% between 2022 and 2028^[1]. The contemporary term pyridine was created by combining the Greek words pyr, which means "fire", and iodine, which is the ending for aromatic amines. In order to create pyridine, William Ramsay heated acetylene and hydrogen cyanide in an iron tube in 1876^[2]. Since pyridine is a planar, six-member heterocyclic ring with five carbons and one nitrogen atom, the nitrogen atom is located in the first desired place in the naming

scheme for the ring. **Figure 1** provides the pharmacokinetic parameters for pyridine derivatives.

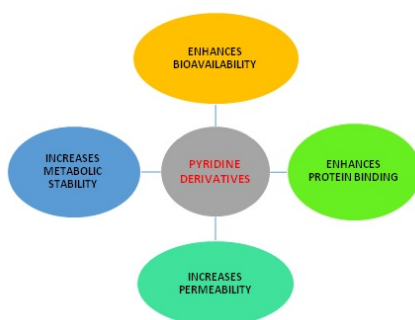


Figure 1. Role of pyridine derivatives on pharmacokinetic parameters.

N-heterocyclic medicines with pyridine or dihydropyridine rings make up around 14% and 4%, respectively, of all approved prescriptions, according to data from the US Food and Drug Administration (FDA). Isoniazid (tuberculosis), Pyridostigmine (myasthenia gravis), Nicotinamide (pellagra), Piroxicam (arthritis), Enpiroline (malaria), Omeprazole (ulcer), Tacrine (Alzheimer's disease), Tropic Amide (anti-muscarinic), Delavirdin (HIV), Nilvadipine (hypertension), etc., all contain pyridine rings and are widely used. **Figure 2** elucidates the function of pyridine derivatives in the creation of novel therapies. **Figure 3** shows newer pyridine molecules, and describes how they are made chemically and what they are used for. The FDA-approved vasodilators Milrinone and Amrinone both have pyridine ring systems in their structures (**Figure 4**).

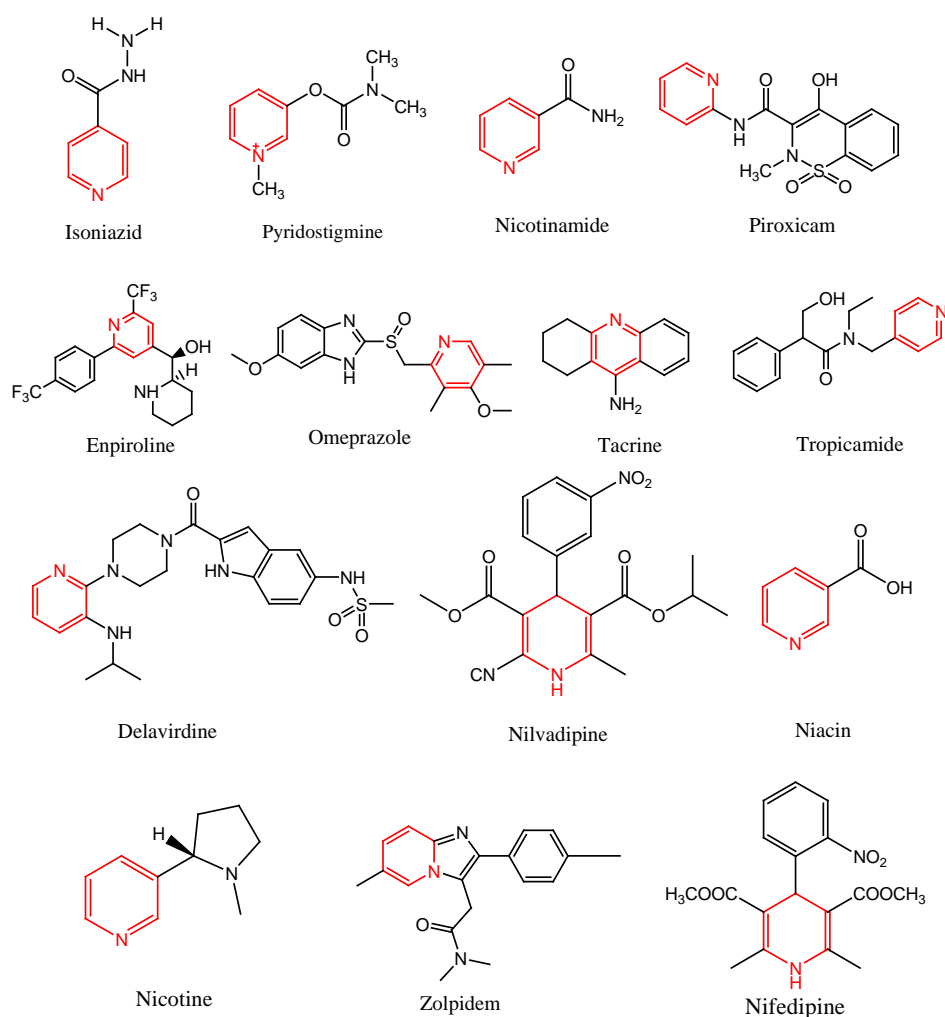


Figure 2. Commercially available drugs having pyridine ring system.

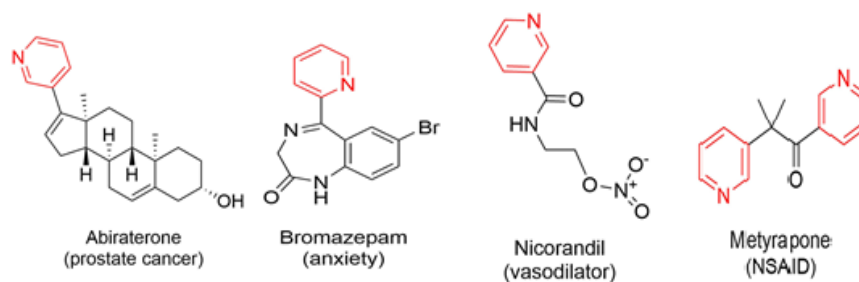


Figure 3. The structure and uses of more recent pyridine molecules.

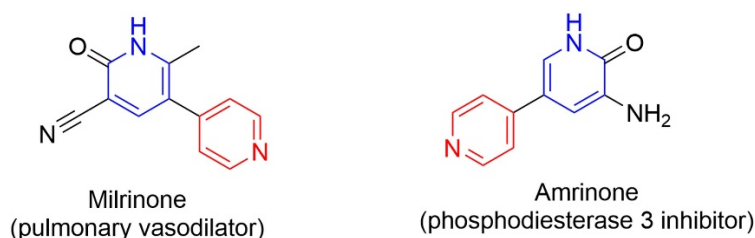


Figure 4. FDA-approved vasodilators with scaffolds made of pyridine.

2. Main text

Pyridine and its derivatives are the building blocks for a wide range of medicines because of their potent biological action. The study's findings offer fascinating instances of drugs with these pharmacological actions (**Table 1**). See **Figure 5** for an illustration of the therapeutic potential of pyridine derivatives.

Table 1. Commercially available drugs indication and its mechanism.

S. No	Drug name	Indications	Mechanism
1	Isoniazid	Tuberculosis	Inhibits mycobacterial cell wall synthesis
2	Pyridostigmine	Myasthenia gravis	Blocks the action of acetyl cholinesterase
3	Nicotinamide	Pellagra	Replenishes cellular energy
4	Piroxicam	Arthritis	Inhibition of cyclooxygenase
5	Enpiroline	Malaria	Inhibition of β -hematin formation
6	Omeprazole	Ulcer	Inhibition of the H^+/K^+ -ATPase system
7	Tacrine	Alzheimer's disease	Inhibition of acetylcholinesterase
8	Tropicamide	Anti-muscarinic	Relaxes the pupillary sphincter muscle
9	Delavirdin	HIV	Binds directly to reverse transcriptase
10	Nilvadipine	Hypertension	Inhibits HMG-coenzyme A reductase
11	Niacin	Hyperlipidemia	Decrease levels of VLDL
12	Nicotine	Withdrawal symptoms	Stimulates presynaptic ACh receptors
13	Zolpidem	Insomnia	GABA _A receptor agonist
14	Nifedipine	Angina	Reduces peripheral vascular resistance.
15	Chloroquine	Malaria	Inhibits the formation of hemozoin
16	Trazodone	Depression	Reduces levels of neurotransmitters
17	Amlodipine	Hypertension	Calcium Channel blocker
18	Amrinone	Heart failure	Phosphodiesterase inhibitor (PDE3)
19	Indinavir	HIV	Inhibits HIV protease
20	Ciclopirox	Ring worm	Topical fungicidal agent

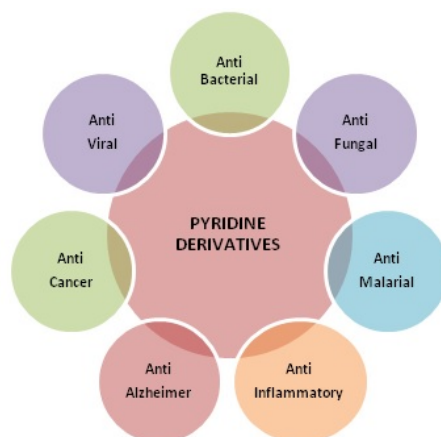


Figure 5. Therapeutic effect of pyridine derivatives.

2.1. Antibacterial agents

The search for new antibacterial medications is being driven by the present global health challenge of antibiotic resistance. The pyridine antibiotic class, which includes medications like ceftaroline, fosamil, ceftazidime, and delafloxacin, has seen widespread use in the past 10 years as a result of the FDA's recognition of their safety and efficacy.

The creation of new antimicrobials, 2-amino-4-aryl-3,5-dicarbonitrile-6-thiopyridines, was announced by Dominik et al.^[3]. The most effective pyridine derivatives against several bacterial strains were used in this experiment based on their susceptibility to lipopolysaccharide (**Figure 6**). Evidently, plasmid DNA may sustain oxidative damage from these pyridine derivatives. We contrasted the harm caused by the selected compounds with the harm caused by conventional antibiotics. The most effective compounds, according to reports, are 5a, 5e, 5f, and 5j^[3]. Reen et al.^[4] designed and synthesized compounds comprising oxazolo[4,5-b]pyridine with the aim of evaluating their antibacterial characteristics (**Figure 7**). Such compounds showed remarkable efficiency against *S. aureus* (methicillin-resistant) when compared to gold-standard drugs like streptomycin and ampicillin. The most potent derivatives were found to be molecules 28 and 31, with MIC values ranging from 1.55 to 25 g/mL. Such pyridine derivatives were said to be more effective against gramme-positive bacteria than gramme-negative bacteria. These substances have also been shown to be effective against different bacterial strains^[4].

Azetidin-2-ones and 4-thiazolidinone Schiff bases were created and synthesized as pyrazolo[3,4-b]pyridine derivatives by Salem et al.^[5] (**Figure 8**). The antibacterial properties of the same compounds were investigated. At dosages of 0.12 to 62.5 g/mL, it was found that practically all drugs produced positive effects. It was discovered that compound 7-b had a MIC of 0.98 g/mL, making it just as effective as the common drug amphotericin B. These substances were discovered to be useful in the discovery of a new class of antibacterial agents^[5]. Khidre et al.^[6] designed and manufactured the thiazole-derived dihydropyridine. The effectiveness of these chemicals against bacteria was studied. Compound 17 was discovered to be extremely active against both *A. flavus* and *C. albicans*, and compound 13a was demonstrated to be highly active against *A. flavus*. It was found that this strength was caused by an electron-withdrawing group, a big phenyl ring, and an inductive action (**Figure 9**)^[6].

2.2. Antifungal agents

Currently, there are more fungal infections that are resistant to multiple drugs. This has pushed medicinal chemists to use pyridine derivatives to find new antifungals (**Figure 10**). Wei et al.^[7] developed and made inulin Schiff bases that have pyridine rings. These derivatives were tested to see if they could kill *P. asparagi*,

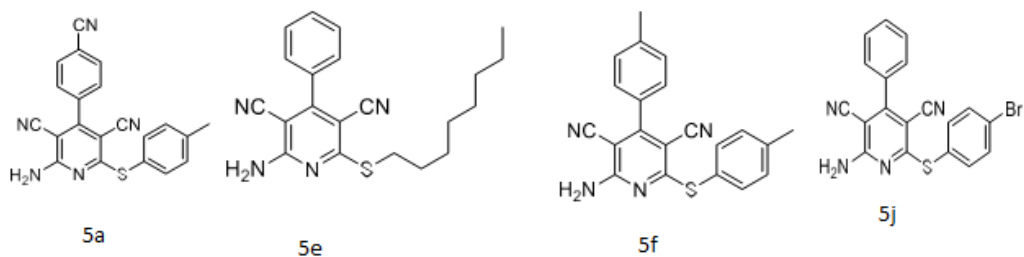


Figure 6. Pyridines as anti-bacterial agents^[3].

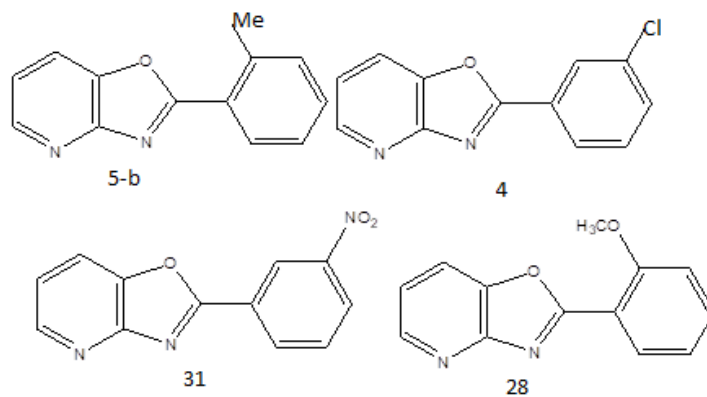


Figure 7. Oxazolo pyridines as anti-bacterial agents.

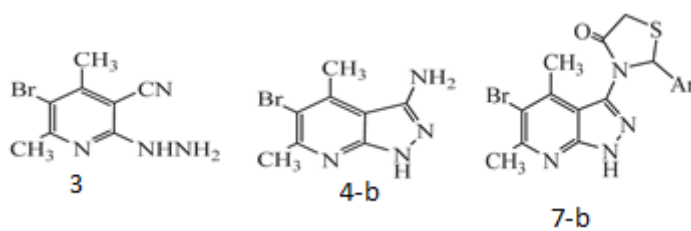


Figure 8. Pyrazolo-pyridine derivatives of 4-thiazolidinone as anti-bacterial agents^[5].

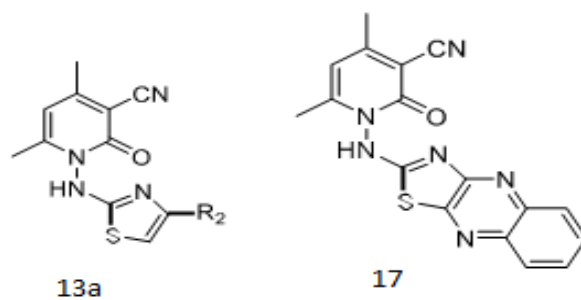


Figure 9. Thiazole-derivative dihydropyridine^[6].

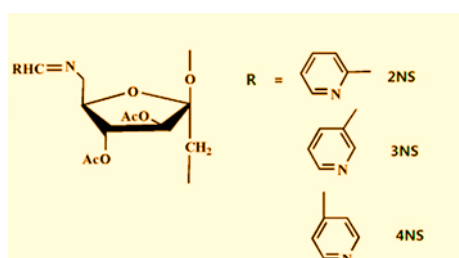


Figure 10. Inulin Schiff bases bearing pyridine rings as anti-fungal agents^[7].

F. oxysporum, and *B. cinerea* in a lab dish. It was found that compound 3NS had an inhibitory index of 77.0% and that at a dose of 2.0 mg/mL, it was very effective at killing *B. cinerea*^[7].

Jia et al.^[8] described how antifungal pyridine-grafted chitosan polymers were created and used. By combining pyridine molecules with chitosan by a nucleophilic substitution procedure, *N*-(1-carboxybutyl-4-pyridinium) chitosan chloride was produced (**Figure 11**). The antifungal effectiveness of these chitosan derivatives was assessed by inhibiting fungus growth. These substances were discovered to have higher levels of antifungal activity than pure chitosan. These substances' minimum inhibitory and fungicidal concentrations (MICs) against *F. fulva* were found to be 0.14 mg/mL and 1 mg/mL, respectively; for *B. cinerea*, the corresponding values were found to be 4 mg/mL and 0.14 mg/mL. It was found that the fungal hyphae's structure was severely injured and distorted by pyridine chitosan, which prevented the strain from growing. These substances are safe antibacterial agents with prospective uses in agriculture and the food business, according to tests on mice's toxicity^[8]. Tan et al.^[9] developed 1,2,3-triazole-pyridine derivatives of starch in **Figure 12**. The effectiveness of these compounds as antifungal agents against the fungi *C. lagenarium*, *W. fusarium*, and *P. asparagi* was tested in experiments. Unexpectedly, it was shown that the antifungal activity of these starch derivatives was significantly greater than that of starch alone against three distinct fungi. Additionally, it was demonstrated that *C. legendarium* could be eliminated at a starch derivative (III) concentration of 1.0 mg/mL. The 1,2,3-triazole's higher antifungal activity may be attributed to the alkylation of its pyridine ring^[9], which is one theory.

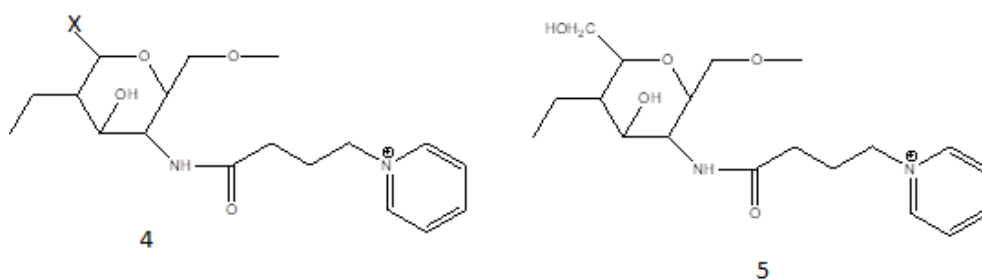


Figure 11. Pyridine-grafted chitosan polymers as anti-bacterial agents.

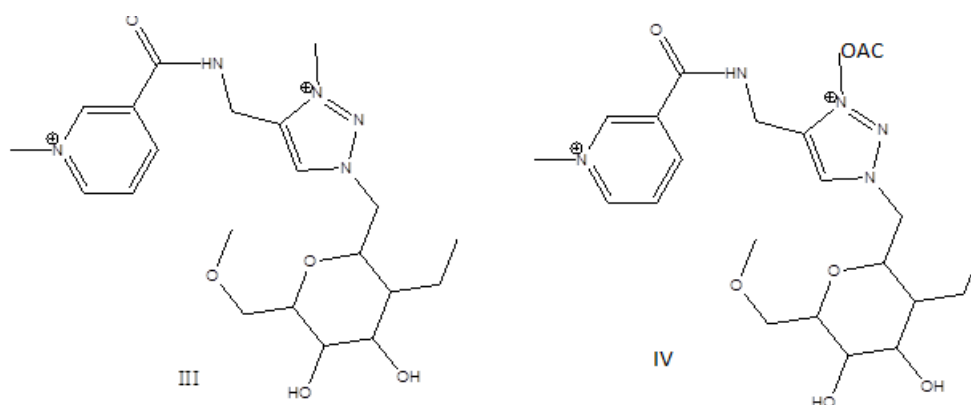


Figure 12. The 1,2,3-triazole-pyridine derivatives.

Using a fragment-based technique, Elshemy et al.^[10] have described a novel family of pyridyl-indole compounds. Comparable substances were examined for their capacity to fend off malaria in isolates of *P. falciparum* that were both chloroquine-resistant and chloroquine-sensitive. Compounds 50–52 were shown to be the most effective against malaria in in vitro tests (IC₅₀ = 1.47–9.23 M for D6 and 1.16–7.66 M for W2)^[10].

2.3. Antimalarial agents

By adding a fosmidomycin moiety, Xue et al.^[11] created pyridine scaffolds (**Figure 13**) that prevented *P. falciparum* from growing. The substance with the highest potency was a derivative, which was eleven times more potent than fosmidomycin. The creation of a hydrogen bond between the nitrogen of the pyridine and the cysteine in the *P. falciparum* protein is thought to be the cause of their antimalarial actions. These substances have also been demonstrated to be effective against bacteria that are resistant to chloroquine^[11]. Adnan and colleagues created and produced several series of pyridine derivatives. On chloroquine-sensitive mice that had *P. berghei* infection, anti-malarial activity was tested in vivo. When given at a dosage of 50 mol/kg, derivatives 2a, 2g, and 2h substantially slowed the growth of parasites. With an IC₅₀ of 0.040 M against chloroquine-resistant *P. falciparum* RKL9 strains, compound 2g has shown promising efficacy^[12].

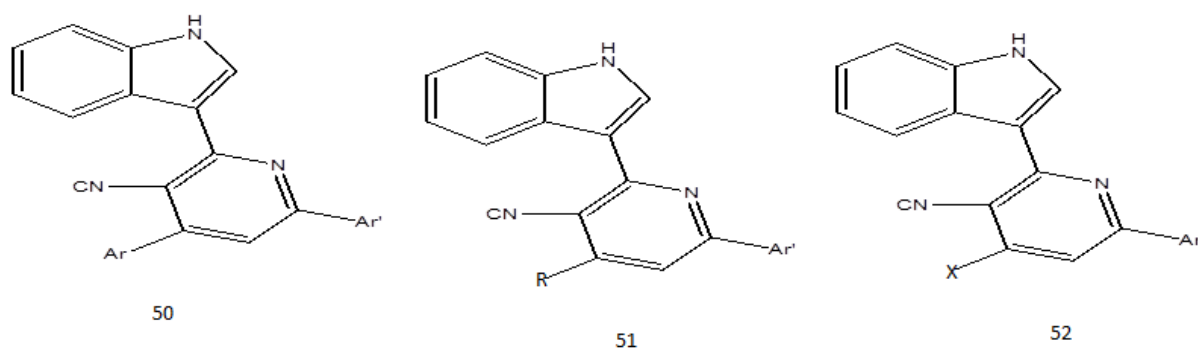


Figure 13. Novel pyridine derivatives as antimalarial agents^[11].

2.4. Antiviral agents

Numerous pyridine derivatives have been shown to have antiviral properties in the scientific literature (**Figure 14**^[13]). Drugs containing pyridine were found to be quite efficient against HIV, HCV, HBV, RSV, and CMV in recent trials. The antiviral efficacy of these medications has been linked to a number of different mechanisms of action, including inhibition of reverse transcriptase, polymerase, maturation, viral thymidine kinase, and DNA/RNA replication. Martinez et al.^[13] created and published significant isothiazolopyridine derivative antiviral activity. The tolerance half-maximum concentrations (IC₅₀) ranged from 0.1 to 0.5 M, according to calculations. Derivative 7d was the most powerful of all the compounds examined, with an IC₅₀ value of 0.124 M. The paraposition of the phenyl ring linked to the pyridine was changed in a number of different ways^[13] to produce antiviral activity.

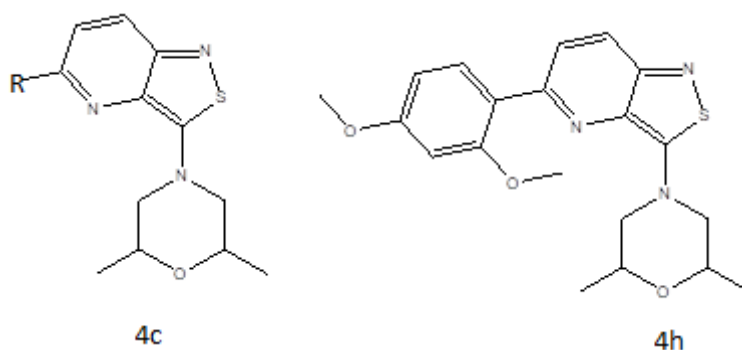


Figure 14. Isothiazolo pyridines as antiviral agents.

In 2020, Wei et al.^[14] reported the synthesis and evaluation of 2-benzoxyl-phenylpyridine derivatives against Coxsackie virus type 3 (CVB3) and adenovirus type 7 (ADV7) (**Figure 15**). These chemicals were found to have remarkable antiviral efficacy against both virus strains, as measured by a decrease in cytopathic effects caused by the viruses. These substances were found to have higher antiviral potencies than the standard

drug ribavirin. Replication, RNA replication, and synthesis of viral proteins were all effectively targeted by these chemicals, indicating that they were specific to CVB3^[14].

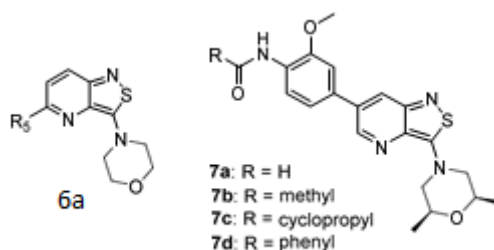


Figure 15. The 2-benzoxyl-phenylpyridine derivatives as antivirals.

New sulfonamide-moiety-containing pyridine derivatives, such as benzothiazole and benzimidazole, were developed and produced by Azzam et al.^[15]. These chemicals were examined for their potential antiviral effects. Herpes simplex virus 1 (HSV-1) and Coxsackie virus 4 (CBV-4) were two viruses that 15a and 15c were found to inhibit by 50% at low concentrations. Azzam and her team made seven new [2,3-b]pyridine compounds in 2017. **Figure 16** looked at how well they stopped the Mayaro virus (MAYV) from spreading in a rodent cell line. At low doses, all of the drugs were able to stop the production of viruses. Through simulated tests, it has been shown that these drugs are safer to take by mouth and are more bioavailable. During the early stages of virus replication, it was found that some of these substances had a strong effect on MAYV. In this work, it was shown that thienopyridine derivatives are effective against alpha viruses^[15,16].

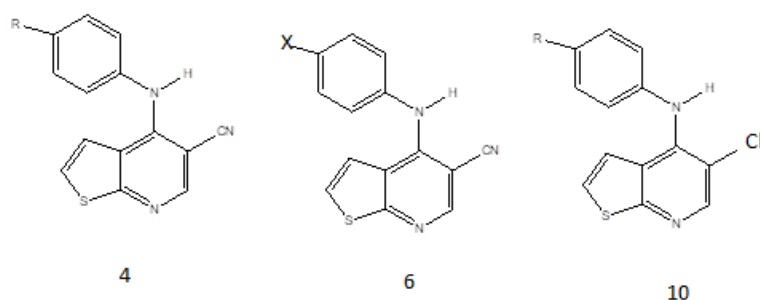


Figure 16. Thieno[2,3-b]pyridine derivatives as antivirals.

2.5. Anti-inflammatory agents

These medications are used to treat muscular and articular inflammatory diseases such as osteoarthritis and rheumatoid arthritis. Yaqoob et al.^[17] created a class of strong anti-inflammatory drugs employing derivatives of Isonicotinic acid, such as pyridine. **Figure 17** demonstrates the extremely high ROS-inhibitory activity of structures 77 and 79. Compound 77 was determined to be the most effective with an IC₅₀ of 1.4 g/ML^[17].

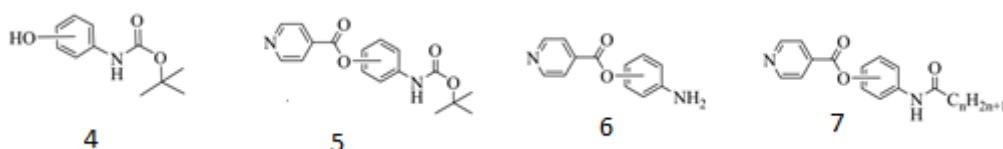


Figure 17. Pyridine derivative as anti-inflammatory agents.

In 2019, Kandasamy et al.^[18] reported that they have developed a chemical that suppresses inflammation by blocking nitric oxide (NO) production at a concentration of 26 micromolar (M). Additionally, we looked at a strategy for reducing inflammation by studying this molecule: its ability to activate Nrf2 (a transcription

factor protein). Compound 159 was found to be a potent activator of the transcription factor Nrf2 (IC₅₀ 4.21 M). Based on NO inhibition and Nrf2 activation, the same chemical was described as the most effective molecule^[18]. For the purpose of P38 kinase inhibition, Ali et al.^[19] designed and synthesized a series of imidazol-5-yl pyridine derivatives. It is well accepted that the intracellular signaling regulator P38/MAPK14 is responsible for the production of a wide variety of inflammatory mediator cytokines, such as TNF- α , IL-1 β , and IL-6. The results of the trials showed that structures 11a and 11d exhibited strong inhibitory activities (IC₅₀: 47 μ M and 45 μ M)^[19]. Synthesis and evaluation of 3H-imidazo[4,5-b]pyridine derivatives with a diaryl pharmacophore were published in 2017 by Kirwen et al.^[20]. There were eight distinct 2,3-diaryl-3H-imidazo[4,5-b]pyridine molecules tested for their COX-inhibitory effects in this study. It was shown that structure 3f was significantly inhibitory of both COX-2 and COX-1, with IC₅₀ values of 9.2 and 21.8 mol/L^[20], respectively.

2.6. Alzheimer's disease

Memory loss and other cognitive impairments are common symptoms of Alzheimer's disease, a neurological ailment. The Alzheimer's disease-fighting ability of a number of reported pyridine compounds has been evaluated.

Haghighijoo et al.^[21] published some benzyl-1H-1,2,3-triazol-4-yl-N-cyclohexylimidazo[1,2-a]pyridin-3-amine derivatives (**Figure 18**). The majority of the substances inhibited BACE1 (β -site amyloid precursor protein cleaving enzyme 1) and BuChE (butylcholinesterase) effectively in in vitro studies. Seven f and seven g, both of which have a dichloro (2,3-Cl₂ and 3,4-Cl₂) group on the benzyl ring, have been reported to have IC₅₀ values of 12 and 8.9 M in the aforementioned enzyme inhibition assay^[21].

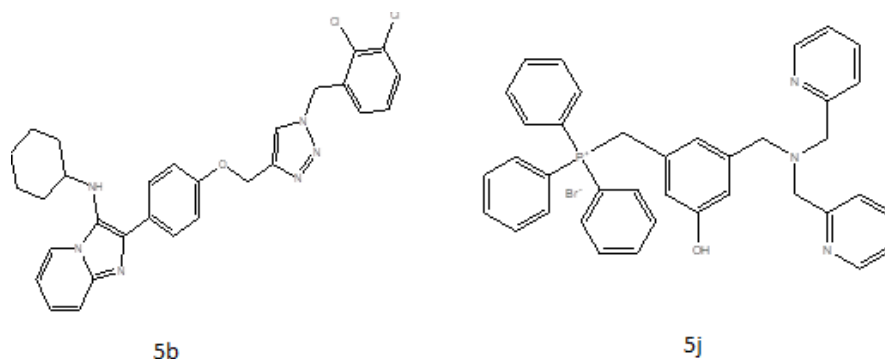


Figure 18. Pyridine derivative that's been shown to be effective in treating Alzheimer's disease.

A pyridine amine derivative (PAT) was created by Zhu et al.^[22] in 2019 as 3-bis(pyridin-2-ylmethyl)aminomethyl-5-hydroxybenzyltriphenylphosphonium bromide. According to the results of western blotting, reverse transcription polymerase chain reaction, and fluorescence imaging tests, PAT made *C. elegans* less paralysed when ROS production was cut down. It also kept mitochondrial expression safe.^[22] In order to better understand how to inhibit cholinesterase, Saeedi et al.^[23] produced [2,3-b]pyridine containing amine derivatives and studied their inhibitory effectiveness. Maximum activity against acetylcholinesterase and butyl cholinesterase was obtained for derivatives 5e and 5d (IC₅₀ values of 1.55 and 0.23 M, respectively)^[23].

2.7. Anti-cancer

The search for novel cancer therapies has made substantial use of the class of heterocyclic substances known as pyridine derivatives. These compounds are well-known for being a potent class of chemicals that can be used to treat a variety of illnesses, such as breast cancer, myeloid leukemia, pancreatic cancer, and liver cancer. The exciting new pyrido [2,1-b]quinazoline derivatives of Bathula et al.^[24] used in vitro anticancer studies employed the NCI-H460, A549, HCT-15, HT-29, HFL, and DU-145 cell lines. Molecule S1 (A549 and NCI-H460) displayed the strongest anticancer efficacy against lung cancer cell lines^[24].

Jian et al.^[25] studied the inhibitory and anti-proliferative effects of 26 newly synthesised pyrazolo[3,4-b]pyridine derivatives of combretastatin. The reactions of the MDA-MB-231, MCF-7, Kyse150, and HeLa cell lines to a select few compounds were relatively moderate (**Figure 19**). The reported compound 6n, which triggered cell arrest in the G2/M phase, was said to be the most effective one^[25]. Hassan et al.^[26] developed 44 new thieno[2,3-b]pyridine derivatives. They were tested in HepG2 and MCF7 cell lines to see how well they killed cancer cells and how they compared to regular doxorubicin. The most action came from compounds 2, 7, 12, and 19. This was true for both cell lines^[26]. Murugavel et al.^[27] wrote about how a thiophene variant with pyridine and 1,2,3-triazole affected living things. The drug-like qualities of BTPT were found by looking at its active pharmacokinetic and pharmacodynamic features (ADMET) in a test tube. Molecular docking was used to select a site on human topoisomerase II that binds to ATP. The MTT experiment was used to measure how fast PC-3, A549, and MDAMB-231 cells grew. When compared to the gold standard medicine, doxorubicin, BTPT was much more effective at stopping cancer in MDAMB-231 (a breast cancer cell), A-549 (a human lung cancer cell), and PC-3 (a human prostate cancer cell). There was hope that BTPT would become a potential new compound for fighting cancer^[27].

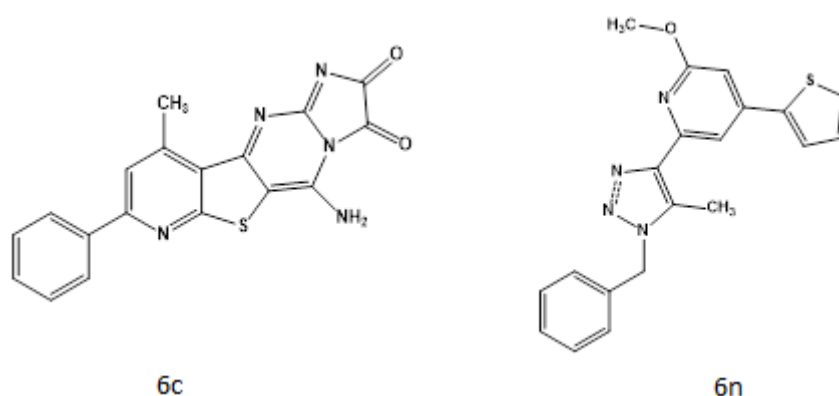


Figure 19. Pyridine derivative as anti-cancer agents.

3. Characterization of pyridine derivatives

3.1. UV-Visible spectroscopy

Due to the presence of different groups (chromophores) in the pyridine ring, pyridine derivatives have many unique bands between 360 and 460 nm. Electron-donating groups absorb light in the range of 390–460 nm, and electron-accepting groups do the same between 360 and 415 nm^[20].

3.2. FT-IR spectroscopy

Fourier transform infrared spectroscopy (FTIR) is a potent method for figuring out the molecular makeup of things in all of their different forms. Important information on the shape and structure of numerous molecules is provided by the simulations' outcomes^[23]. The FTIR spectrum shows unique peaks at particular wavelengths, such as (C=N) 1560–1655 cm^{-1} , (C=C) 1593–1598 cm^{-1} , and (C=O) 1680–1700 cm^{-1} , when the pyridine ring is functionalized in various ways.

3.3. NMR-spectroscopy

When different groups are substituted on the pyridine ring, the chemical shift values of the protons and carbon atoms alter. Between 6.5% and 9.2% of hydrogen can be detected in pyridine molecules per mole^[28]. The pyridine ring's electron-donating group in position 3 (8.05–9.00 ppm) causes the ¹HNMR peak in the range. The pyridine proton appears between 7.55 and 9.00 ppm when there is a carbonyl group between the pyridine and the other aromatic group at position 3. The proton in the second pyridine ring is the least shielded proton. The presence of an amide functional group at position 2 results in proton peaks in the range

of 8.30–8.38 ppm, whereas the presence of a bulky group at position 2 results in proton peaks in the range of 7.67–8.75 ppm^[29]. Despite the proton at position 6 normally being deshielded to 8.75^[30], the proton peaks of the pyridine ring are reported as being in the range of 7.60–9.2 ppm due to the presence of an alkyl group at position 3. The proton occurs between 7.94 and 8.82 ppm^[26] when a 4-position alkyl group or more replacements are present. Carbons contained in pyridine often exhibit ¹³C NMR signals between 121 and 165 ppm. Normally, the carbon at positions 3 and 5 is deshielded to 149 ppm^[26].

4. Conclusion

The pyridine moiety is unique due to its extensive range of biological functions. Due to their potent antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and other medicinal actions, pyridine derivatives are widely used in medicine. A pyridine derivative is currently the most commonly used medication. Pyridine derivatives can effectively inhibit a wide range of biological receptors. A pyridine nucleus with varied substitutions is the source of biological activities, including viral problems, microbial disorders, and the diversity of tumour cells. The striking therapeutic properties of pyridine derivatives have inspired medicinal chemists to create more potent chemotherapy medicines. The clinical use of pyridine drugs to treat a variety of illnesses has increased. There are numerous ways to synthesise pyridine, and the structural modifications that may be made to it provide tremendous potential in the area of medicinal chemistry.

Author contributions

Conceptualization, MAA and SKM; methodology, KE; software, KSN; validation, CA; formal analysis, SS; investigation, MAA; resources, KE; data curation, SKM; writing—original draft preparation, KE; writing—review & editing, SKM.

Conflict of interests

The authors declare that there is no conflict of interest.

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