IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Title:- "Pyridine: Synthesis, Swiss-ADME and Applications."

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Abstract

Pyridine, a significant heterocyclic compound present in various natural products, plays a crucial role in medicinal advancements. Noteworthy drugs, such as Omeprazole (1998) and Netupitant (2014), have utilized the pyridine ring system to combat diverse human ailments, including cancer-related nausea. Recent FDA-approved anticancer drugs like Abemaciclib (2015) and Ivosidenib (2019) highlight the ongoing progress in pyridine-based research. This review explores the latest developments in pyridine chemistry and its coordination complexes, assessing the medicinal efficacy of both organic and inorganic derivatives. Our discussion includes selected biological applications, showcasing the enduring promise of pyridine in addressing various disease-related challenges.

Keywords: Heterocyclic, Hantzsch, Chichibabin, Bohlmann-Rahtz, Conard-Limpach, Bonnemann, SWISS-ADME

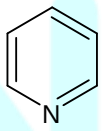
Introduction

Pyridine, with the chemical formula C5H5N, belongs to the order of heterocyclic organic composites. Its structural resemblance to benzene is apparent, featuring a six-membered aromatic ring where one CH group is substituted through the artistic touch of a nitrogen heteroatom. The region features a conjugated system hosting six π -electrons, reminiscent of benzene, dispersed throughout the heterocyclic ring. Firstly deduced from coal tar extraction, pyridine's contemporary production involves the synthesis from formaldehyde, ammonia, and acetaldehyde: (1)

$$NH3 + CH2O + 2CH3CHO \rightarrow C5H5N + 3H2O$$

Functioning as a crucial solvent and reagent in organic synthesis, pyridine finds utility in Knoevenagel condensations. Its versatility extends to being a widely used polar and aprotic solvent, demonstrating miscibility with various solvents, including hexane and water. (2)

While inherently colorless, pyridine can adopt a yellow hue in older or impure forms, linked to the evolution of elongated, unsaturated polymeric chains, flaunting notable pulsating with electrical vitality. The pyridine ring plays a pivotal role in an array of crucial compounds contributing to their significance, spanning agrochemicals, medicinals, and vitamins. Although historically deduced from coal tar, the contemporary global conflation of pyridine stands at roughly 20,000 tons annually as of 2016. (3)



Pyridine

Synthesis of Pyridine

Hantzsch Pyridine synthesis.

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).

• **Requirements-**

1. Beta-ketoester (eg. Ethyl acetoacetate)

2. Aldehyde

3. Ammonia / Ammonium acetate

4. Acidic catalyst (glacial acetic acid)

5. Ethanol

6. Distillation apparatus

Procedure

To a RBF, 1 mole of Beta-ketoester + I mole of aldehyde + excess of ammonia + add Small amount of acidic catalyst.

Heat the reaction mixture under reflux condition allow the reaction to proceed for several hours.

After reaction completed cool it.

Transfer reaction mixture into separating funnel & extract the pyridine into organic solvent, typically ethanol.

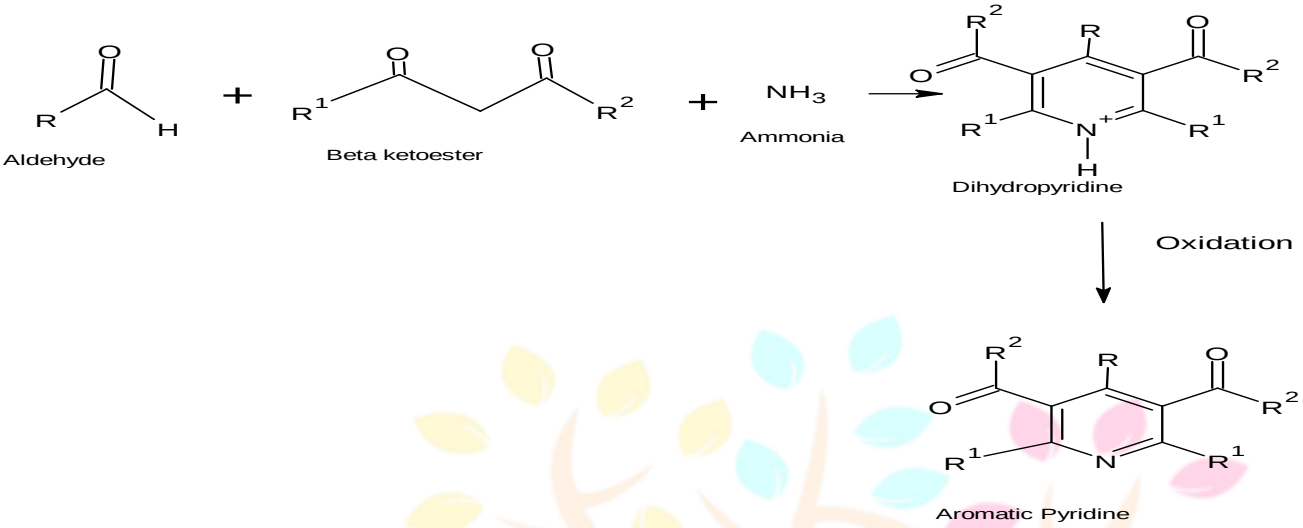
Wash the organic layer & with water & remove any impurities.

Dry it with anhydrous salt (anhydrous sodium sulfate) carefully evaporate the organic solvent to obtain the crude pyridine.

The crude pyridine can be further purified by distillation to obtain pure pyridine.

Collect the pyridine fraction in the receiving flask during distillation & store it in an appropriate Container. (4) (5)

Reaction



Chichibabin Synthesis.

It Involves the reaction of primary amines with Alpha, Beta- unsaturated Compounds. (6) It was reported by Aleksei Chichibabin in 1924. (7) (8)

Material needed

1) Primary amine (eg. aniline)

2) alpha, beta-unsaturated compound (eg. acrolein)

3) Base (eg. Sodium ethoxide).

4) solvent (eg. Ethanol)

Procedure

In a suitable reaction Vessel mix 1 mole of primary amine + I mole of alpha, beta-unsaturated compound.

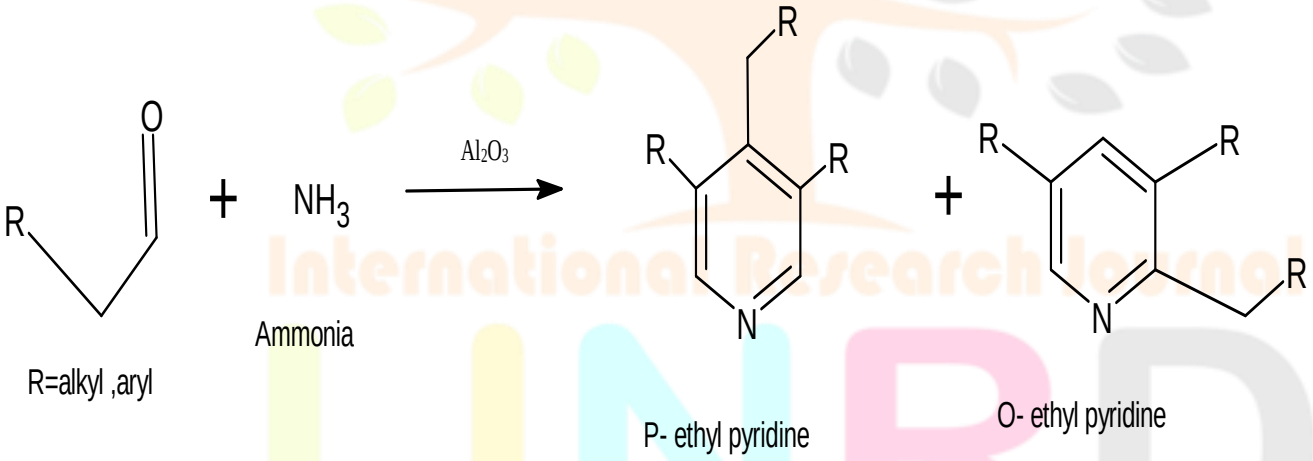
Introduce a strong base to the mixture. The base serves of a catalyst for reaction.

Heat the reaction mixture & stir it to promote the reaction typically occurs at elevated temperature.

The reaction proceeds via the format of an intermediate known as a pyridinium salt, followed by a rearrangement to produce pyridine.

After reaction complete cool the mixture & neutralize any remaining base. The resulting solution can be subjected to extraction and purification steps to isolate the pyridine product.

Reaction



Bohlmann – Rahtz pyridine synthesis-

Bohlmann –Rahtz pyridine conflation is a response that generates replaced pyridines in two way, first a condensation response between an enamine and an ethynylketone to form an aminodiene intermediate, which after heat convinced E/Z isomerization go through a cyclodehydration to yield 2,3,6-trisubstituted pyridines. (9) (10) (11) (12)

Chemical Requirements

1) Nascence, Beta-unsaturated Carbonyl emulsion (eg. Alpha, beta-unsaturated ketone)

2) Primary amine (19 aniline)

3) Aldehyde (eg formaldehyde)

4) Acidic catalyst (eg acetic acid)

5) Solvent (eg. Ethanol)

6) Reaction vessel with Reflux condenser

Procedure

Mix alpha, beta-unsaturated carbonyl compound + Primary amine + aldehyde in desired molar ratios you may also add acidic catalyst.

Heat the reaction mixture under reflux condition

steps in reaction-

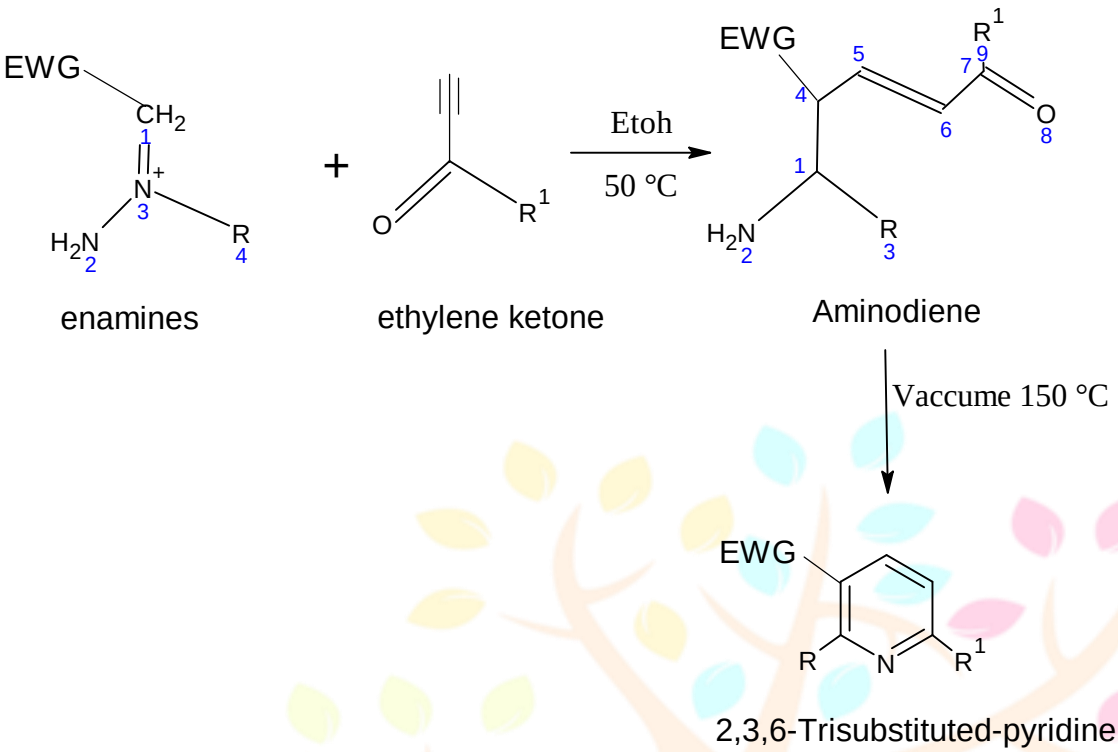
First primary amine & aldehyde form an imine intermediate & it undergoes. Cycloaddition like reaction with alpha, beta-unsaturated carbonyl compound to form the pyridine ring.

After reaction completed cool it & transfer the reaction mixture to a separating funnel & extract the pyridine product into an organic solvent.

Wash the organic layer with water to remove any impurities or by products. Then dry the organic layer using anhydrous salts. To remove any remaining water.

Carefully evaporate the organic solvent to obtain the crude pyridine product. If high purity is required, further purification can be achieved through column chromatography / distillation.

Reaction



Conard – Limpach Synthesis

The reaction involves the condensation of an alpha, beta-unsaturated aldehyde with ammonia & a compound containing a nitrogen atom. (13)

Reagents

1) Alpha, Beta-unsaturated aldehyde (eg. Acrolein)
2) Ammonia
3) Compound Containing a nitrogen atom (eg hydroxylamine)

Procedure –

Mix alpha, beta-unsaturated aldehyde + ammonia + emulsion containing a nitrogen snippet

Toast the response admixture to boost the condensation response. leading to the conformation of pyridine.

After response is complete, cool the admixture. & quench any unreacted material if necessary.

Insulate the pyridine product from the response admixture, generally by birth & also purify if demanded.

Bonnemann Cyclization –

This involves the use of a 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. (14)

Reagents

1) Alkyne compound with a nitrogen containing substituent
2) metal complex Catalyst (eg. Nickel)
3) Suitable ligands
4) Solvent

Procedure-

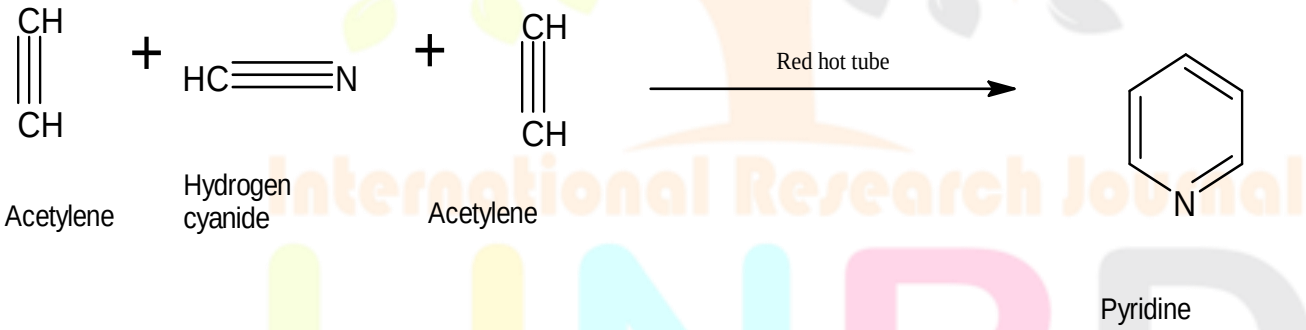
Under inert conditions mix the alkyne compound, metal complex catalyst, ligand and solvent

Heat the reaction mixture under controlled conditions, often at elevated temperature.

The metal complex facilitates the cyclization of the alkyne compound, leading to the formation of the Pyriding ring

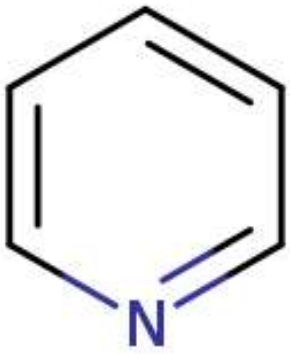
Cooled it, isolate pyridine product from mixture, typically by extraction & further purification if required.

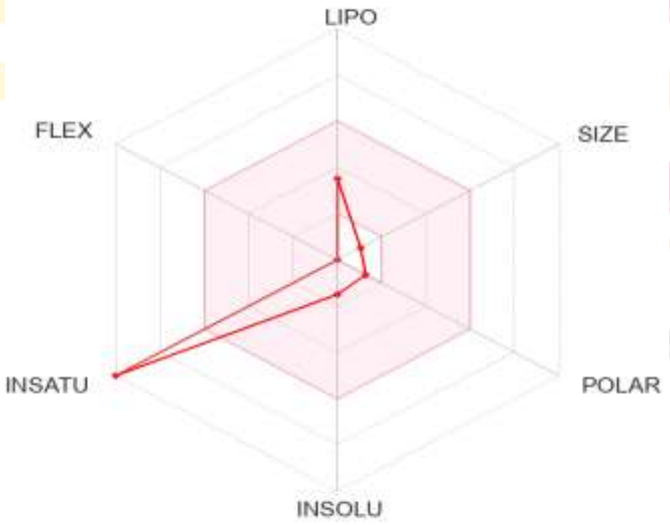
Reaction



SWISS-ADME

The Swiss ADME (Immersion, Distribution, Metabolism, and Excretion) profile of pyridine encompasses its characteristics in terms of drug-related properties. Evaluation of pyridine's absorption, distribution within the body, metabolic transformations, and excretion processes is crucial for understanding its pharmacokinetic behavior. This comprehensive analysis aids in assessing the potential of pyridine in drug development and its suitability for therapeutic applications. (15) (16)





Formula	C5H5N
Molecular weight	79.10 g/mol
Number of heavy atoms	6
Number of aromatic heavy titles	6
Fraction Csp3	0.00
Number of rotatable bonds	0
Number of H-bond acceptors	1
Number of H-bond donors	0
Molar Refractivity	24.24
TPSA	12.89 A2

Table no.: 1

Physical & Chemical Properties (15)

GI immersion	High
BBB permeation	Yes
P-gp substrate	No
CYP1A2 asset	No
CYP2C19 asset	No
CYP2C9 asset	No
CYP2D6 asset	No
CYP3A4 asset	No
Log Kp (skin saturation)	-6.32 cm/s

Table no. : 2

Chemical Kinetics (15)

Log S (ESOL)	-1.48
Solvability	2.62e+00 mg/ml ; 3.31e-02 mol/l
Class	Very solvable
Log S (Ali)	-0.50
Solvability	2.52e+01 mg/ml ; 3.19e-01 mol/l
Class	Very solvable
Log S (SILICOS-IT)	-1.90
Solvability	9.91e-01 mg/ml ; 1.25e-02 mol/l
Class	Solvable

Table no.: 3

Water Solvability (15)

Applications of Pyridine

Anti-microbial

Novel pyridine derivatives, such as di-acylhydrazine and acyl(arylsulfonyl) hydrazine, exhibit potent antimicrobial properties. Their antibacterial efficacy against both gram-negative bacteria, E. coli, and gram-positive bacteria, S. albus, surpasses that of the standard medicine streptomycin sulphate. These derivatives have demonstrated promising potential as dressings against a spectrum of plant pathogens, including C. dactylon, C. rotundus, E. crusgalli, E. hirta, C. argentia, E. indica, and T. procumbens. Furthermore, their antifungal activity against A. niger and A. teniussiama, benchmarked against Griseofulvin, underscores their multifaceted therapeutic applications.(17) (18)

Anti-viral

Oxime derivatives of thiazolo(5,4-b) pyridine demonstrate significant efficacy against influenza B-mass contagion. Furthermore, oxime derivatives of pyridine and naphthiridine exhibit potent antiviral activity against HIV, with recent findings indicating their antibacterial effects. Notably, oximes derived from naphthiridine also show promise in combating bacterial infections. Pyridine-derived oximes serve as curatives for poisoning by organophosphorus compounds. In the context of antiviral interventions, hydrazone compounds derived from 3 and 4-acetyl pyridine, known for their anti-tumor effects, effectively inhibit the replication of HCV for both RNA(+) and RNA(-) strains. Additionally, bipyridinyl derivatives complexed with ruthenium display robust antiviral activity against hepatitis C contagion (HCV). (19) (20)

Antioxidant

Certain thiopyridine derivatives showcase a captivating duality, not only embracing antioxidant prowess (SOD) but also unveiling cytotoxic effects (DPPH) in a seductively distinctive manner. The dynamic interplay between their SOD and DPPH activities unfolds as an explosive reflection of their underlying molecular structures. Intriguingly, in-depth QSAR studies unravel that dipole moment and electrophilic indicator stand out as paramount descriptors intricately weaving the molecular intricacies with their distinct SOD activities. This intricate dance reveals that molecules boasting elevated dipole moment and electrophilic indicator values are orchestrated for heightened SOD

efficacy. Furthermore, a fascinating revelation emerges as compounds wielding the minutest infinitesimal polarizability (MATS4p) ascend to claim the pinnacle of DPPH efficacy. (21)

Anti-Diabetic

In the intricate realm of medicinal exploration, the pyridine derivatives, adorned with thiazolidinones, gracefully march forth, unveiling their ballet of antidiabetic influence within a GOD-covered system. Amidst this chemical performance, a select cadre of these compounds emerges as virtuosos, orchestrating veritably effective anti-diabetic conditioning. Their nuanced dance on the molecular stage not only hints at perceptible anti-diabetic prowess but also raises the curtain on a potential avant-garde in the realm of diabetic therapeutics—a tantalizing glimpse into the prospect of a revolutionary class of anti-diabetic medicines yet to unfold. (22)

Anti-Cancer Activities

In the alchemical interplay of copper(II) essence complexes with the Schiff base 2-[N-(a-picolyl)-amino]-benzophenone, particularly those stemming from brominated pyridine products, a symphony of remarkable cytotoxicity emerges, reaching unparalleled heights. This chemical crescendo extends to unveil not just potent but veritably exceptional antitumor exertion, painting a canvas of promise in the quest for innovative cancer interventions. (23) Composites harmonizing pyrazoline, pyridine, and pyrimidine with the intricate touch of indole functionality were achieved in a commendably pure state. These compounds, upon scrutiny, were revealed to exert excellence in combating excrescence cells, hinting at a promising avenue in the pursuit of effective anticancer agents.(24)

Topoisomerase I and II impediments

In the intricate dance of molecular interactions, the Bobby(II) complex, adorned with a nitrogen-containing heterocyclic thiosemicarbazone, emerges as a virtuoso, deftly inhibiting topoisomerase II and orchestrating a formidable barrier against the proliferation of bone cancer cell lines. Enter the stage, 4-pyridyl anilinothioaazol (PAT), a key player in the therapeutic narrative, casting its healing aura specifically against Von Hippel Lindall (VHL)-induced excrescence in renal cell lymphomas. This not only signifies a breakthrough but paints a unique chemotypic canvas, unveiling a targeted approach poised to redefine the landscape of RCC treatment. (25)

Anti-Malarial Agents

Several blends of pyridine quinoline composites as hybrid molecules were evaluated for their effectiveness against a chloroquine-susceptible strain of Plasmodium falciparum. The findings indicated that these molecules exhibit limited anti-malarial activity. However, the composites suggest potential as templates for developing new anti-malarial medications, and their efficacy could be enhanced. Additionally, these molecules demonstrated inhibition of haem polymerization. (26)

Anti-Inflammatory Innovations

A cluster of imidazo(1,2-a) pyridine variations, crafted akin to emulsion 37, showcase distinctive anti-inflammatory attributes. The amalgamation of 2-acetyl pyridine and 4-acetyl pyridine with select amides unveils noteworthy prowess in anti-inflammatory actions. (27)

Analgesic Potential

In the realm of analgesic exploration, synthesized heterocyclic compounds featuring pyridine nuclei, particularly those within the range of 38-40, showcased analgesic prowess akin to the benchmark drug (pentazocine). Notably, the presence of mecamylamine on the heterocyclic ring revealed characteristics of exertion retardation. (28)

Neurochemical Interplay

In the intricate dance of psychopharmacology, the complex [Cr(ox)2(2-(aminomethyl) pyridine)] and 1,10-di(4-octylaminopyridinium-1) decane dichloride showcase a unique bioavailability for biomolecules in non-aqueous realms. The strategically placed functional groups carry a profound significance, skillfully forming bonds with diverse biomolecules. Meanwhile, derivatives of 6-methyl-2-(phenylethynyl)-pyridine (MPEP) maintain an intriguingly nuanced psychopharmacological negative influence. (29)

Amoebic Alchemy

Derived from acetyl pyridine, certain ligands showcase a latent anti-amoebic prowess. However, their union with ruthenium(II) in a complex catapults their anti-amoebic efficacy to remarkable heights, as exemplified by the exceptional performance of complex 41 surpassing the standard metronidazole. In the realm of vanadium, a bi-

nuclear complex, featuring 2-acetylpyridine, unveils a striking amoebocidal impact with an IC50 value of 1.68-0.40, outshining even metronidazole (IC50 value of 1.81), while intriguingly, the ligand in isolation exhibits no inherent anti-amoebic influence. (30)

Anti-arrhythmatic exertion

The seamless fusion of pyridine and pyrimidine derivatives with a thiophene moiety was explored. Subsequent testing of the derived compounds for antiarrhythmic effects demonstrated superior efficacy compared to standard antiarrhythmic agents such as Procaine amide and Lidocaine.(31)

Staphylococcal Alchemy

Embarking on the quest for anti-staphylococcal agents, the derivative 3-aminopyridine, a pyridine kin, engages in a transformative polymerization process. The emergent polymer not only showcases anti-staphylococcal prowess but adds a unique note to the symphony of antibacterial exploration. Curiously, the free state of 3-aminopyridine remains inert, yet its polymerized form, especially in petite oligomers, orchestrates heightened effectiveness. Unveiling a molecular weight ballet, the antibacterial performance of the polymer takes center stage in this microbial symphony. (17) (18)

Iron Load Alleviation

The pyridine derivative, pyridine-2-carboxaldehyde isonicotinoylhydrazone (PCIH), forms highly stable complexes with iron, resulting in a potent chelator. The derivatives of this ligand, when used individually, serve as drugs for managing iron load complaints. Interestingly, the original ligand itself exhibits therapeutic properties comparable to the standard medicine, deferoxamine. (32)

Enzymatic Mastery In the intricate realm of enzyme inhibition

Benzimidazole derivatives with a pyridine ring exhibit inhibitory effects against gastric H/K-ATPase. Within the realm of enzyme modulation, a series of imidazo(1,2-a)pyridine derivatives, including specific composites, demonstrate the capacity to inhibit acyl-CoA (cholesterol acyltransferase), offering valuable insights into diverse enzymatic control mechanisms. (32)

Conclusion

In the alchemical tapestry of chemistry, pyridine derivatives stand as veritable magicians, orchestrating a symphony of natural operations. Their role in medicine is nothing short of pivotal, with these compounds displaying a captivating spectrum of activity against an array of natural targets, from microbial miscreants to elusive viral foes and the intricate realm of cancerous cells. The pyridine derivatives, akin to shape-shifters, navigate the intricate dance of molecular substitution, linking with enzymes, proteins, and the very essence of DNA, sculpting a unique narrative in the grand tapestry of natural problem-solving.

Conflict of interest – None declared

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