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Pyridazine: A Magical Moiety

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Abstract

Introduction: A heterocyclic organic molecule having the chemical formula, C4H4N2. It is aromatic and has a 6-membered ring with two nearby nitrogen atoms. It has a specific heat of 208 °C and is an inert liquid. This paper presents a complete summary of the phytochemical and pharmacological activity of pyridazine as well as its derivatives published to date using new research findings and a wide variety of data.

For the study, authors' scientific journal articles on pyridazine as well as its derivatives were investigated.

The pharmacological properties of pyridazine as well as its derivatives include anti-cancer, anti-hypertensive, anti-allergic, anti-histaminic, eosinophil chemotaxis-inhibiting, anti-inflammatory, anti-PAF (thrombin factor), anti-HIV, and anti-histaminic effects.

Conclusion: Pyridazine and its derivatives are involved in many pharmaceutical procedures. Although researchers have highlighted the crucial roles pyridazines and its derivaives that fulfills, we emphasize that further laboratory studies should be conducted in order to broaden the breadth of this compound's possible applications.

Keywords: Pyridazine, Antioxidant, Antibiotic, Anti-inflammatory

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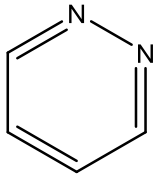
1. Introduction

Pyridazine is a chemical compound with the molecular formula $C_4H_4N_2$, also known as 1, 2-diazine . It is a 6-membered ring with two nearby nitrogen atoms. Its molar mass is 80.09 gm mol-1. 1.107 gm/cm^3 is the density of it. Orthodiazine, oizine, and 1, 2-diazine are further names for it. (1)

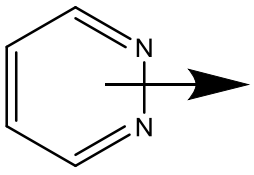


Structure of Pyridazine

Figure 1. Structure of Pyridazine

2. Physical Properties of Pyridazine

Pyridazine is a neutral liquid with a boiling temperature of 207°C. The pair of electrons on the nitrogen atom forms hydrogen bonds with protonated solvents and benzene. It is only weakly basic, and basicity is increased by electron-donating groups (pKa-2.3). Thus, 4-methyl yridazine has a pKa value of 2.93. Pyridazine has a dipole moment of 3.9 Debye. (2)



Dipole moment of Pyridazine

Figure 2. Dipole Moment of Pyridazine

3. Chemistry of Pyridazine

The molecule of pyridazine that resembles pyridine is lacking in. These molecules are more water soluble than other hydrocarbons due to the presence of π-deficient nitrogen aromatic heterocyclic compounds. Pyridazine's

basic aromatic ring structure features two nitrogen atoms close by. The nitrogen atoms in this molecule perform unique chemistry. (3) Because they contain a lot of nitrogen atoms, these molecules can link with a good substrate. (2)

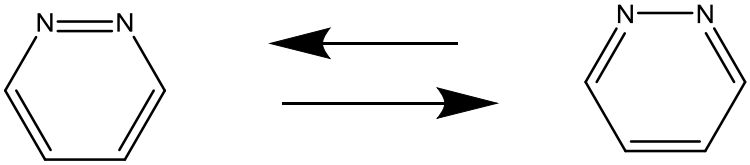


Figure 3. Resonating Structures of Pyridazine

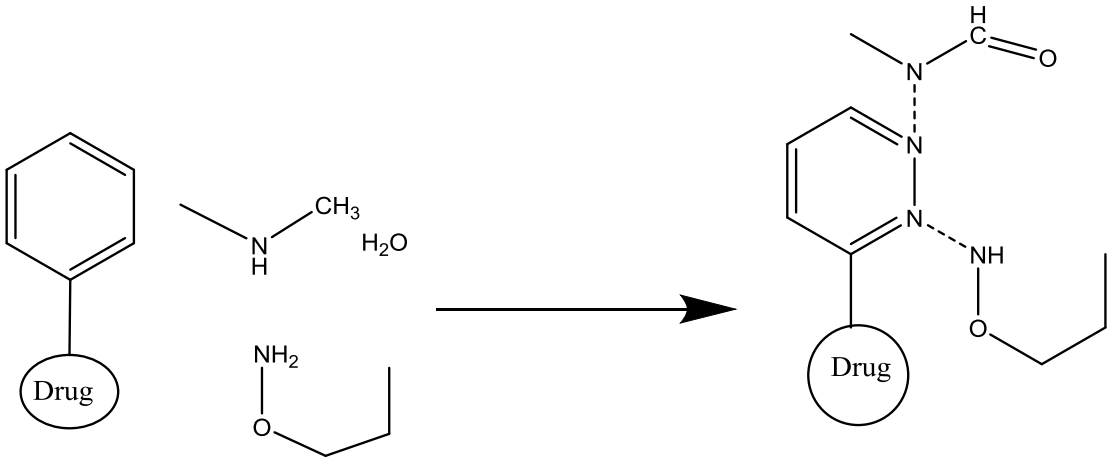


Figure 4. Interaction of Pyridazine containing drugs with receptors

Six reduced Pyridazines are possible; the Pyridazine is thought to be a plane six-membered ring.

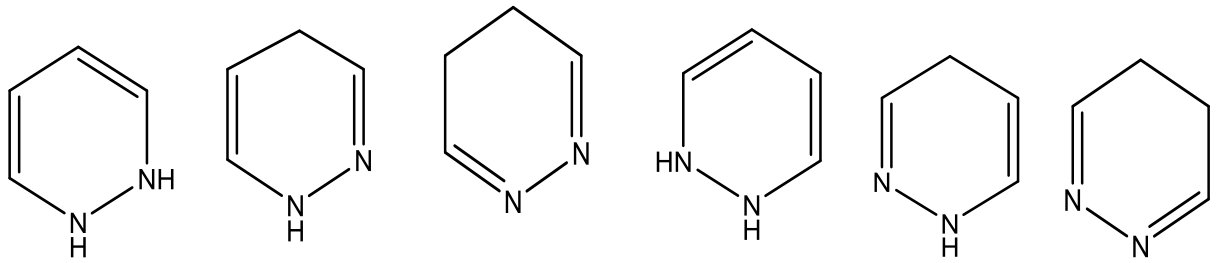
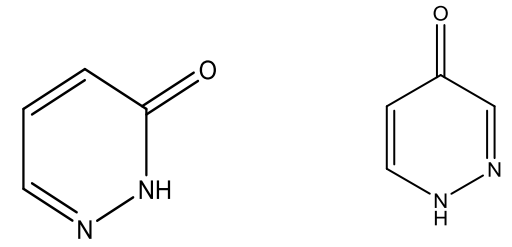


Figure 5. Reduced Pyridazines

That substituted pyridazine exhibits tautomerism. As a consequence, 3- & 4-hydroxy pyridazines are more common in the oxo form. In Figure, the 3- & 5-hydroxypyridazine-1-oxides are shown in their hydroxyl-N-oxide forms, as well as the 4- and 6-hydroxypyridazine-1-oxides in their N-hydroxypyridazinone forms. (3)



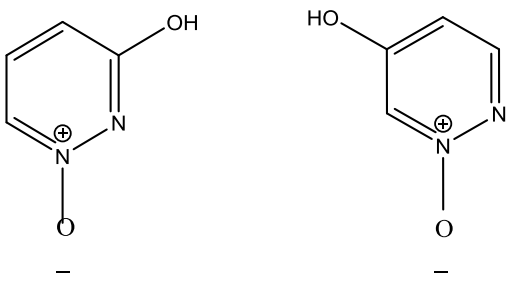
Pyridazin-3(2*H*)-one

6a

Pyridazin-4(1*H*)-one

6b

Figure 6. Hydroxy Pyridazines



3-hydroxy-1-methylpyridazin-1-ium 7a

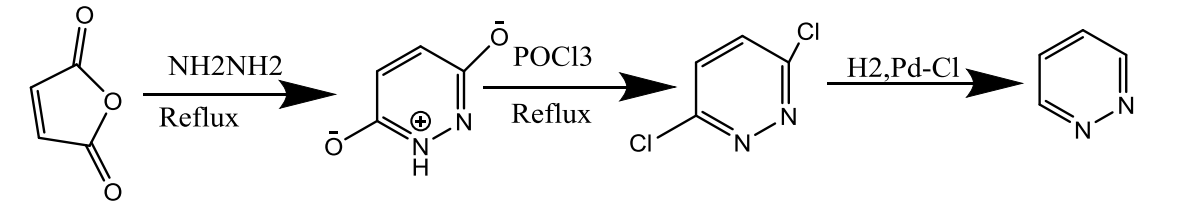
5-hydroxy-1-methylpyridazin-1-ium 7b

Figure 7. Pyridazine-1-oxides and Pyridazones

4. Synthetic Methods

Pyridazine was found by Fischer in 1886, and Tauber produced it for the very first occasion in 1895. (4) Tauber had to oxidize 3,4,5,6-dibenzopyridazine in order to produce pyridazine, and then he had to decarboxylate the resultant pyridazine tetracarboxylic acid. Gabriel and Colman produced the parent 1,2-diazine with a low yield after starting with 2-(p-ethoxybenzoylpropionic acid). (5) However, the majority of modern pyridazine manufacturing relies on either using benzoylacetate or hydrazine or its derivatives in combination with the appropriate 1,4-disubstituted carbon chain. (6)

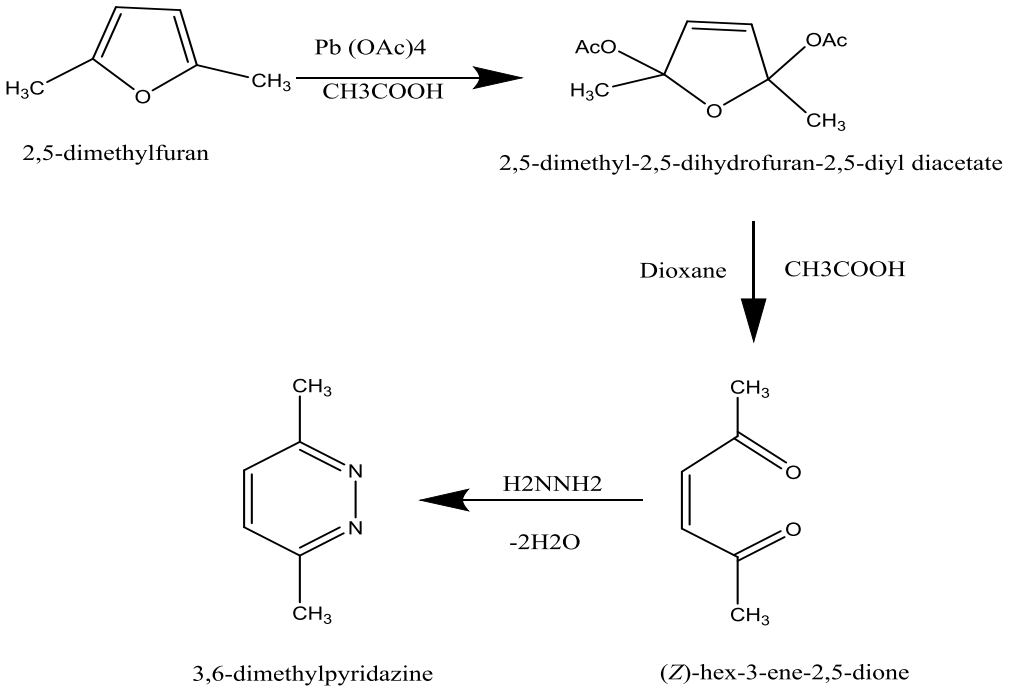
From Maleic Anhydride: When hydrazine or its derivatives are combined with 1,4-dicarbonylethenes, butenilides, or dihydrofuran, pyridazine rings are created. Pyridazine is created by refluxing dichloropyridazine with phosphorus oxychloride after the intermediate has been dehalogenated using hydrogen over Pd-C. (7)



Furan-2,5-dione — Pyridazin-1-ium-3,6-bis(olate) — 3,6-dichloropyridazine — Pyridazine

Figure 8. Synthesis of Pyridazine from maleic anhydride

From compounds containing 1,4-dicarbonyl: Alkyl substituted pyridazines are most frequently produced by simple one-step cyclization about an unsaturated diketone as well as hydrazine. (8)



2,5-dimethylfuran — 2,5-dimethyl-2,5-dihydrofuran-2,5-diyl diacetate

3,6-dimethylpyridazine — (*Z*)-hex-3-ene-2,5-dione

Figure 9. Synthesis of pyridazine from dicarbonyl compounds

3. From 1,2,4,5- Tetrazines: By cycloadditioning 1, 2, 4,5- Tetrazines with alkenes, pyridazines are created. This approach was created by Carboni and Lindsey. (9)

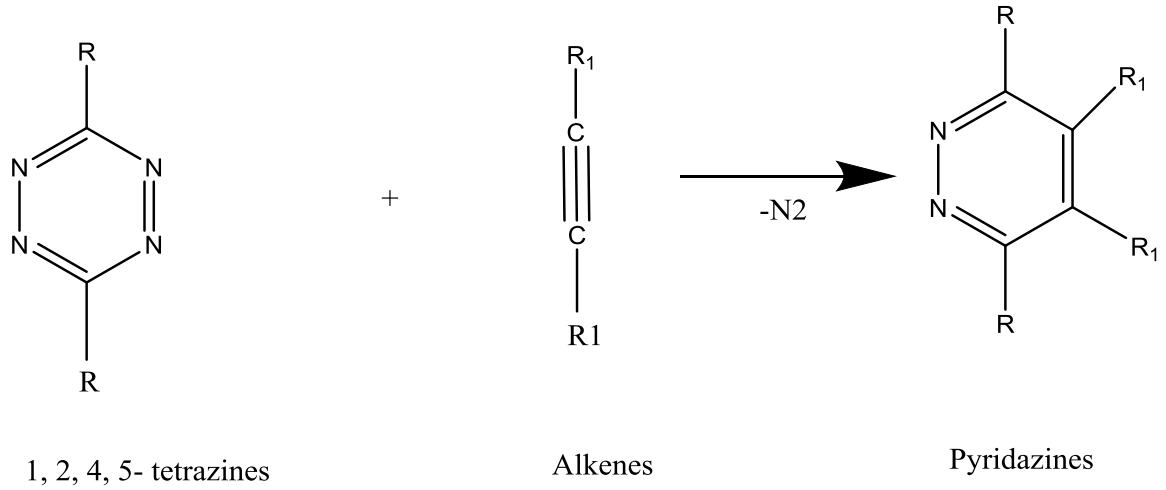


Figure 10. Synthesis of pyridazine from tetrazines

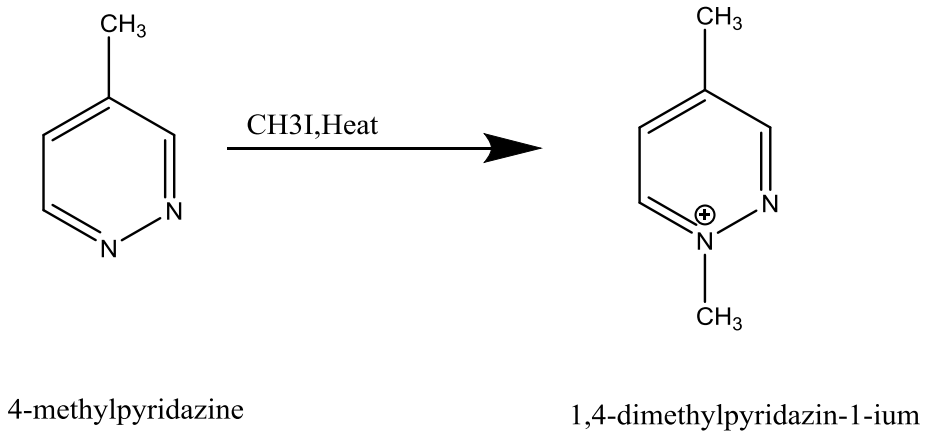


Figure 11. Alkylation of pyridazine at N-1 position

5. Chemical Reactions

a). Reactions with Acids: Pyridazine interacts with minerals acids to generate salts since it is a weak basic. It is difficult to hydrolyze the second nitrogen atom because it requires a lot of energy to generate two positive charges on adjacent atoms.

b). Quaternization: The pyridazine ring reacts with an alkyl halide as well as dialkyl sulphate in the vicinity of a base to generate mono quaternary ions, though far less quickly than pyridine. The location of monoalkylation depends on the alkyl groups on the ring. In the following procedure, the methyl group regulates the alkylation of 4-methylpyridazine to the N-1 position. (10)

c). Electrophilic Substitution: The pyridazine nucleus' electron deficient 3-, 4-, 5-, and 6-positions are brought about by the inductive impact of nitrogen atoms. Only under extremely difficult conditions does reaction take place since pyridazine itself is very resistant to electrophilic substitution. Pyridazine hasn't been sulfonated or nitrated, according to any sources. Furthermore, it is unlikely that pyridazine will be directly halogenated, which is a method that is not expected to be widely applied.

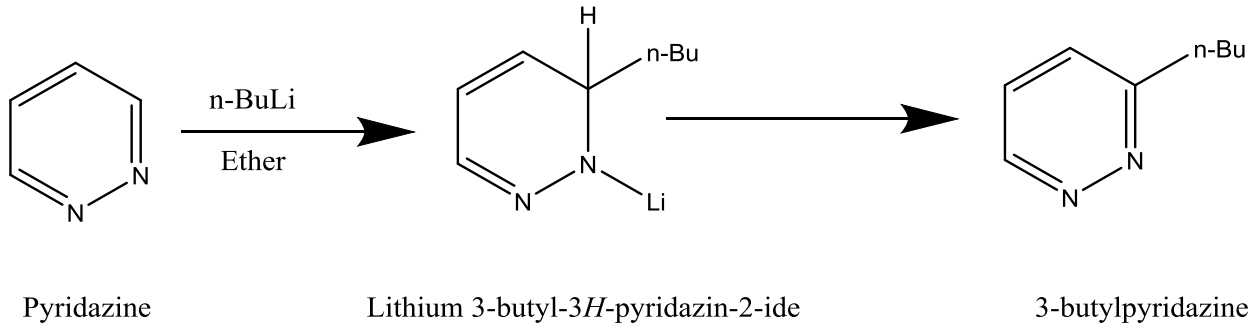
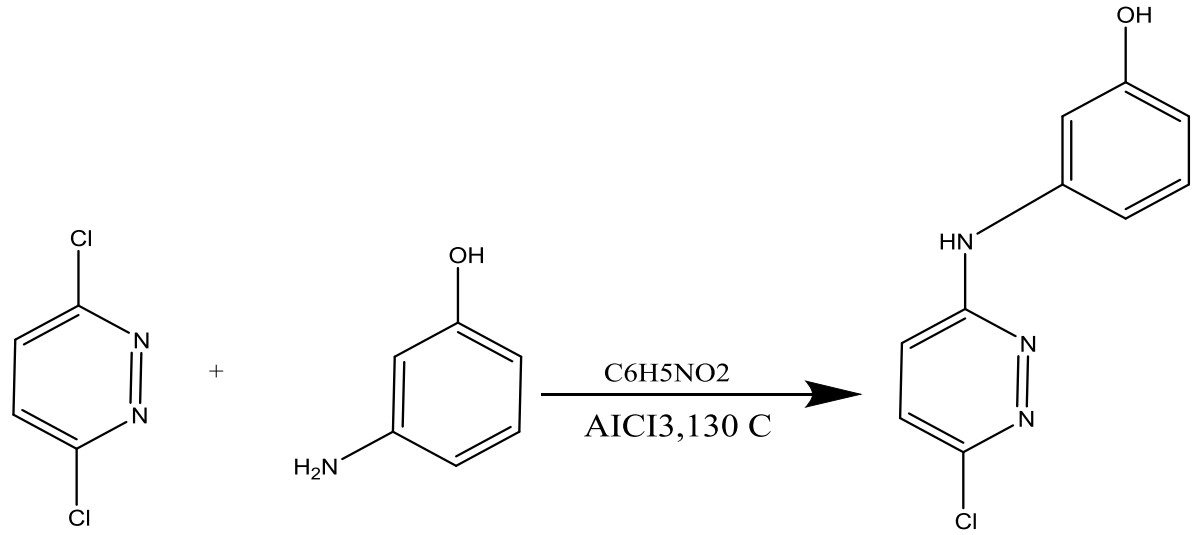


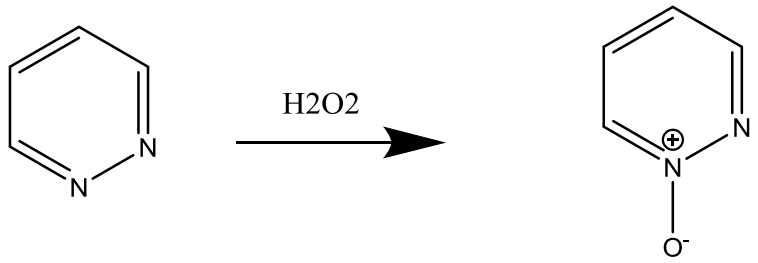
Figure 12. Reaction with Nucleophilic Agent

The chemical 3,6-dichloropyridazine can be arylated to create 3-chloro-6-(3-hydroxyamino) pyridazine with the aid of strong aromatic nucleophiles like 3-aminophenol.



3,6-dichloropyridazine 3-aminophenol 3-((6-chloropyridazin-3-yl)amino)phenol

Figure 13. Arylation of 3,6-dichloropyridazine

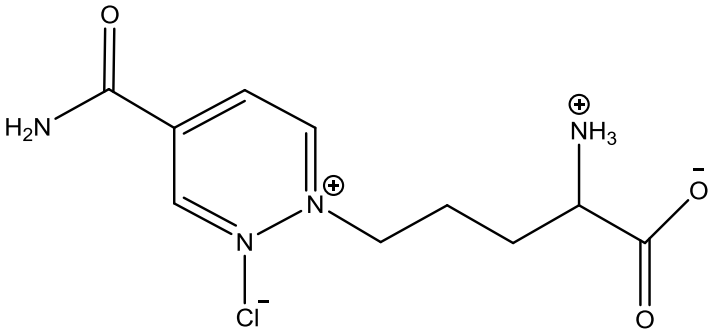


Pyridazine Pyridazine 1-oxide

Figure 14. Reaction of pyridazine with hydrogen peroxide

d). Nucleophilic reagent action on diazine: Diazine is generally quite vulnerable to the effects of nucleophilic reagents. The impact of the extra nitrogen atom is to increase the electron deficit of the carbon atoms in the ring over that of pyridine. Aminopyridazines are produced when copious ammonia or amines are used to directly displace the halo groups. In contrast, Pyridazine interacts with conversely, engages in C-3-position interaction with organolithium. (11)

e). Reactions with Oxidizing & Reducing Agents: Pyridazine is immune towards the assault of oxidizing agents because the ring has insufficient electrons. N-oxide does not form when hydrogen peroxide is used, but N-oxide does. (2)



2-ammonio-5-(4-carbamoyl-2-chloro-1λ^4,2λ^4-pyridazin-1-yl)pentanoate

Figure 15. Pyridazomycin a Natural Antibiotic

6. Natural Pyridazines

Lead structures are frequently obtained from the biochemistry of bioactive substances. Surprisingly few natural substances possess the typical N-N bond observed in pyridazine compounds. The majority of them were identified from broths that were used to grow Streptomyces. The first naturally occurring completely unsaturated Pyridazine is the new antifungal medication pyridazomycin, which is made by the Streptomyces violaceoniger sp. griseofucus. (2)

7. Biological Activity of Pyridazine Analogues

A phenyl moiety can be found in the structure of over half of drug molecules. By substituting these heterocyclic rings with pyridazines, thousands of diaza derivatives are made accessible. There are more possibilities for interactions when pyridazine substrates are employed rather than phenyl scaffolds. (2) Pyridazine derivatives are useful as a preventative or therapeutic for conditions like asthma, allergic rhinitis, and urticarial because of their anti-cancer, anti-hypertensive, anti-allergic, anti-histaminic, eosinophil chemotaxis-inhibiting, anti-inflammatory, anti-PAF (platelet-activating factor) activity, anti-HIV activity, anti-histaminic, and similar properties. (12) The pyridazine structure is present in many herbicides, such as maleic hydrazide, pyridafol, credazine, and pyridate. Cilazapril, cadralazine, minaprine, hydralazine, and cefozopran are other pharmaceuticals that contain pyridazine. (3) Pyridazine-3-one is one of the mystical moiety's many biological effects. There is a larger focus on developing NSAIDs with such a pyridazine nucleus. (13)

Anti-Inflammatory Activity

Inflammation is the biological response of vascular tissues towards noxious stimuli, including such allergens, pathogens, or harmed body cells. Inflammation leads to the onset of diseases including atherosclerosis, rheumatoid arthritis, as well as vasomotor rhinorrhea if left untreated. The dynamic process of inflammation involves proinflammatory cytokines like tumor necrosis factor (TNF), interleukin (1L), as well as the vascular endothelial growth factor (VEGF). (13)

The activities of many NSAIDs have been examined using numerous test systems, and the findings show that most NSAIDs possess higher activities versus COX-1 or COX-2. Inhibitors of the enzymes MAP kinase, GST (glutathione 5-transferase), and NF-k activation have also been shown to have anti-inflammatory effects. (13)

Antimicrobials

Recent increases in the prevalence of pathogen strains resistant to antibiotics have prompted the emergence of innovative, multi-resistant bacterial stains. It is required to look for chemicals in other sources as a result. Pyridazine can serve as a reservoir of potential antimicrobial compounds because it has been found that its derivatives have strong antibacterial and antifungal effects. (14)

Antimicrobials are the many classes of compounds that work to eradicate microorganisms. (15) Both their antibacterial efficacy and modes of action differ. Most of them exhibit various physicochemical and pharmacological traits. (16) In the past, antibiotics have been utilized to treat illnesses, saving many lives. (17) Contrasting to antifungal, antiviral, and antiparasitic treatments, the bulk of anti-infective drugs are antibacterial chemotherapy. Modern mankind has been rationally influenced by this science. The first efficient antibiotic, Salvarsan, was developed by Ehrlich in 1910.

The most effective drugs then came from other categories of antibiotics, including such penicillins, sulfonamide, and beta-lactam antibiotics. (18)

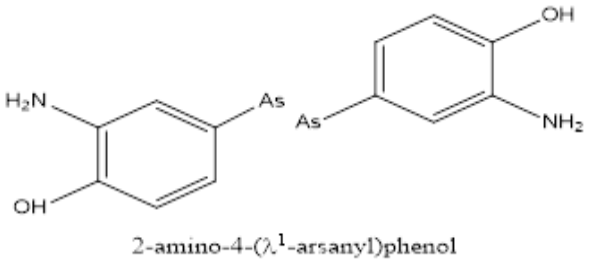


Figure 16. Structure of Salvarsan

8. Classification of Antibiotics

The creation developing antibiotics for the management of bacterial infections has been one of the most important medical developments in the previous 50 years. Although there are other ways to classify antibiotics, the most popular one would be predicated on distinct chemical structures. Beta-lactams, macrolides, tetracyclines, quinolones, aminoglycosides, sulphonamides, oxazolidinones, & glycopeptides are a few of the more well-known antibiotic classes. (19)

Mechanism of Action of Antibiotics

- Reduction in the synthesis of cell walls.
- A decline in the structure or operation of the cell membrane.
- Inhibiting proteins from being made by preventing the structure and operation of nucleic acids.
- Interfering with crucial metabolic processes.
- Disruption of the cytoplasmic membrane and an increase in permeability (20)

Antibiotic Resistance and Need for new Antibiotics

Since tolerance to antimicrobial medications has been discovered to be a substantial obstacle to the medical diagnosis and treatment of many diseases, scientific intervention is required to put certain control mechanisms into place. (20)

Only a few factors can cause microorganisms to become resistant to antibiotics. The main strategies for the existence of a vulnerable microbial population include genetic abnormality, emergence of a latent resistant genes, & transfer of genomes with resistant strains. Several of the traits are passed down through families, while others arise as a result of unintentional

modifications to the microorganisms' DNA. Drug resistance frequently involves the enzymes lactamases, acetylases, adenylases, and phosphorylases. But the revelation of bacterial antibiotic resistance calls into question the therapeutic application of already accessible drugs and forces the creation of brand-new antibacterial substances. The progressive chemistry-based augmentation of antibiotic drugs and bacterial genome searches for prospective therapeutic targets are two techniques for identifying new drug targets that have become popular. It is vital to research unique chemical compounds in order to develop new drugs. This approach to drug discovery is illustrated using ideas from pharmaceutical design and the development of synthetic drugs or compounds. (18)

Antioxidant Activity

Antioxidants are molecules that delay, halt, or inhibit the degradation of substances that are potentially oxidized and help lower oxidative stress by scavenging free radicals. They fit into a variety of chemical categories. Recent research has been done on the antioxidant capacities of pyridazinone derivatives. Because there is evidence linking reactive oxygen groups and nitric oxide to tissue damage and/or inflammation in inflammatory & arthritic disorders, it was thought that substances having combined antioxidant and anti-inflammatory actions would have been essential for the inflammatory diseases. Based on these findings, many compounds of 2H-pyridazine-3-one and 6-chloropyridazine exhibiting anti-inflammatory action were examined in vivo for their ability to produce superoxide, and their effects on lipid peroxidation were compared to those of α-tocopherol.

The bulk of the compounds have a powerful inhibitory effect on the superoxide radicals (among both at 84% and 99%) at a level of 10^{-3} M. Furthermore, these compounds showed action similar to that of α-tocopherol at dosages of 10^{-3} M.

Lipids, proteins, and DNA are vital biological components that can experience oxidative damage. This damage can speed up aging and be the cause of a number of diseases, including cancer, atherosclerosis, rheumatoid arthritis, as well as ischemic injury. (21) Oxidative stress is the term used to describe a scenario when the amounts of reactive oxygen species (ROS) such as superoxide radical anion, hydrogen peroxide, as well as hydroxyl radical are higher than what is necessary for normal cellular functions as well as surpass antioxidative defense capability and repair.

Superoxide, peroxynitrite, and hydrogen peroxide are all detected by dione in isolated mitochondria as well as cell free systems. 8-amino-5-chloro7-phenylpyrido[3,4-d] pyridazine-1,4-(2H,3H pyrrolo [1,2-b] significantly inhibiting lipid peroxidation in vivo are pyridazines with five replacements. (22) There is evidence linking ROS as well as nitric oxide to rheumatic and proinflammatory diseases as inflammatory mediators. (23) Monitoring alterations in skeletal performance carried on by infections and inflammation requires the presence of free radical species. Many chronic diseases share inflammation and oxidative stress as their underlying causes. Especially in the case of neurodegenerative illnesses, inflammatory process continues to play a significant role in the progression of disease. (24) Aminopyridazine has the ability to obstruct inflammatory and oxidative cytokine pathways. (25)

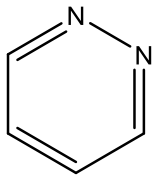


Figure 17. Structure of Pyridazine

9. Structure-activity relationship (SAR)

- The presence of the hydrazinyl, dioxypyrazolidine, and thioamide moieties in the molecules respectively showed their peak antioxidant activity.
- Recognizes the stabilization of nitrogen as well as oxygen atom free radicals.
- The pyrazole moiety is acknowledged to be more active than quinolone and indole rings. Pyridazine thus has antioxidant properties. (26)

10. Conclusion

According to the data compiled in this review, pyridazine and its derivatives have a number of positive effects, including those of an antioxidant, antibiotic and anti-inflammatory drugs. This assertion might yet provide fresh opportunities for therapeutic interventions. To examine key problems in theory, research, and practice about pyridazine as well as its analogues within the health sciences, additional in vitro and in vivo studies are necessary.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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