

Synthesis and Biological assessment in Pyridazine analogues

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Abstract - As a consequence, several of the synthesised compounds demonstrated moderate to good microbiological activity against various strains of microbes and fungus. This was in comparison to the activity of the conventional medicine. This reaction has a number of major benefits, such that it only requires one pot, has an easy work-up approach, produces great yields in a shorter amount of time, and does not require column chromatographic purification. Antimicrobial activity of every recently synthesised chemical were tested against a variety of bacterial and fungal species. A diverse assortment of intriguing pyrazoles have been created as potential candidates for use in the treatment of cancer. The molecule known as pyrazole is a five-membered heterocyclic ring that contains two nitrogen atoms that are located close to each other. There is a wide variety of chemotherapeutic uses for heterocyclic compounds that feature a pyrazole linkage. Anti-inflammatory, antibacterial, antimalarial, antihypertensive, antituberculous, antiviral, neuroprotective, antidepressant, and anticancer activities were only some of the various biological effects that were represented.

Keywords - Pyridazine, synthesis, chromatographic, Biological

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INTRODUCTION

Two nitrogen atoms are located adjacent to one another in the five-membered heterocyclic compound known as pyrazole. There are several chemotherapeutic uses for pyrazole-tethered heterocyclic molecules. Numerous other biological activities, including those that were anti-inflammatory, anti-bacterial, anti-malarial, anti-hypertensive, anti-tubercular, antiviral, neuroprotective, antidepressant, and anti-cancer, were also found. Many pyrazole substances have been tried in clinical trials, and some of them have been useful in the development of potent chemotherapy medicines. The market is flooded with pyrazole-based drugs, including Celecoxib, Apixaban, Fipronil, Betazole, Tepoxalin, Fezolamine, Pyrazomycin, Fomepizole, Mepirizole, Difenamizole, Lonazolac, Tolpizapazole, Crizotinib, Ruxolitinib, and many more. [1]

There are two popular pyrazole-based anticancer medications: crizotinib and roxolitinib. Prostate cancer experimental models have revealed that celecoxib has an anticancer effect. Numerous cancer cells, including those from the breast, prostate, lungs, and stomach, were shown to have undergone apoptosis. Pyrazoles have the potential to treat cancer by suppressing the following proteins: EGFR, topoisomerase II, VEGF, HDAC, IGF-1R, Aurora-A

kinase, cMet, tubulin, mTOR, B-raf, ROS1, CDKs, PI3K, and JAK2. For the action of non-small cell lung cancer, crizotinib is a dual cMet/ALK inhibitor. Myeloproliferative neoplasm is treated with roxolitinib, (JAK2). A inclusive variety of fascinating pyrazoles have been created as potential chemotherapeutic agents. [2]

Compound 1 shows anticancer action against NCIH460, OVCA, AGS, and SW620 human cancer cells, with GI50 values of 0.73, 0.67, 0.79, and 0.89 M, respectively.

With the chemical formula C₄H₄N₂, pyridazine (Figure 1), commonly known as 1, 2-diazine, is a heteroaromatic organic molecule. The CAS number for it is 289-80-5. There are 80.09 g mol⁻¹ in its molar mass. Pyridazine weighs 1.107 grammes per cubic centimetre. 1, 2-diazine, orthodiazine, and oizine are some of its alternate names. [3]

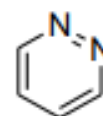


Figure 1: Structure of pyridazine

Dimensional characteristics of pyridazine

Pyridazine has a boiling point of 207°C and is an inert liquid. With protic solvents and benzene, hydrogen bonds are formed via the lone pair on the nitrogen atom. Basicity is strengthened by electron donating groups, and it is mildly basic (pK_a -2.3). Thus, the pK_a value of 4-methyl pyridazine is 2.93. The dipole moment of pyridazine is 3.9 Debye. [4]

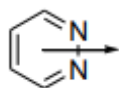


Figure2: Dipole moment of pyridazine

Chemistry of pyridazine

The pyridine-like molecule of pyridazine is a π -deficient substance. When compared to other hydrocarbons, these molecules are more soluble in water because they contain π -deficient nitrogen aromatic heterocycles. Pyridazine has two nearby nitrogen atoms in its fundamental aromatic ring structure. The chemistry of this molecule is made special by the nitrogen atoms. [5]

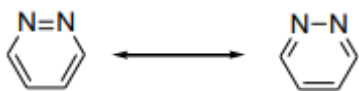


Figure 3: Resonating Structures of pyridazine

These compounds can interact with a suitable substrate due to the numerous nitrogen atoms present in them.

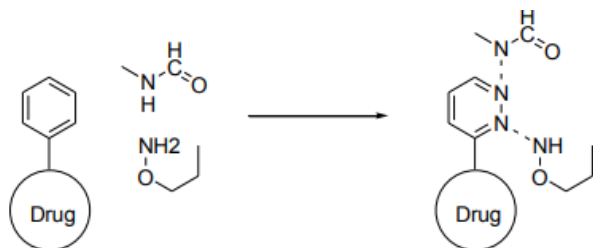


Figure 4: Interaction of pyridazine containing drugs with receptors

There are six potential reduced Pyridazines, with the pyridazine presumed to be a planar six-membered ring. (Figure 5).

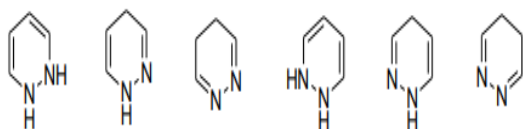


Figure 5: Reduced pyridazines

It has been discovered that substituted pyridazines display tautomerism. Thus, the oxo form is the prevalent one for the 3- and 4-hydroxy pyridazines (figure 6). In contrast to the 4- and 6-hydroxypyridazine-1-oxide, which are mostly found in the N-hydroxy pyridazinone forms, the 3- and 5-hydroxypyridazine-1-oxides occur in the hydroxyl-N-oxide forms (Figure 7). [6]

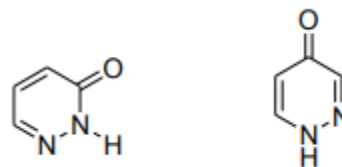


Figure 6: Hydroxy pyridazines

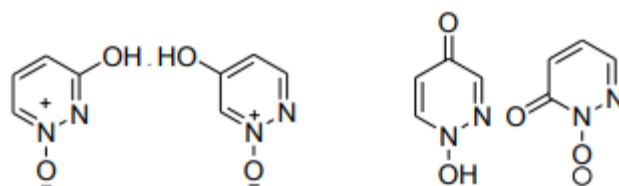


Figure 7: Pyridazine-1-oxides and pyridazinones

CHEMICAL REACTIONS

i. **Reaction with Acids:** Being a weak base, pyridazine reacts with mineral acids to create salts. It takes a lot of energy to produce two positive charges on nearby atoms, making it challenging to protonate the second nitrogen atom. [7]

ii. **Quaternization:** Although less often than pyridine, the pyridazine ring can produce mono quaternary salts by reacting with an alkyl halide or dialkyl sulphate in the presence of a base. Alkyl groups on the ring have a role in where monoalkylation takes place. The alkylation of 4-methylpyridazine is directed to N-1 position in the subsequent reaction by the methyl group. [8]

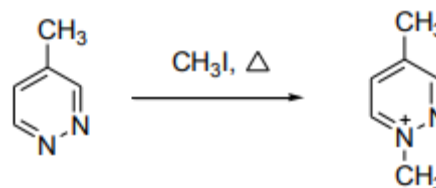


Figure 8: Alkylation of pyridazine at N-1 position

iii. **Electrophilic Substitution:** Due to the inductive influence of nitrogen atoms, the pyridazine nucleus is electron-deficient at locations 3, 4, 5, and 6. Since pyridazine itself is extremely resistant to electrophilic substitution, reaction only occurs under extreme circumstances. There haven't been any reports of pyridazine being sulfonated or nitrated. Additionally, it is not anticipated that the

direct halogenation of pyridazine will be a widely used technique. [9]

iv. Reaction with Nucleophilic reagents: In general, the effect of nucleophilic reagents on the diazine is extremely sensitive. The inclusion of a second nitrogen atom has the effect of depleting the carbon atoms in the ring's ring even more electrons than they already are than they were in the pyridine. The direct displacement of the halo groups with concentrated ammonia or amines results in aminopyridazines, which are then synthesised. At the C-3 Position, pyridazine and organolithium do, however, react. [10]

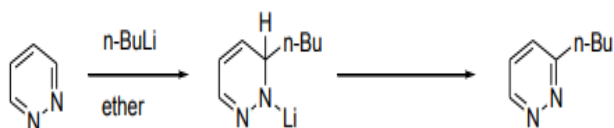


Figure 9: Reaction with Nucleophilic Agent

Three-chloro-6-(3-hydroxyamino) pyridazine is produced via the arylation of 3,6-dichloropyridazine by strong aromatic nucleophiles such as 3-aminophenol.

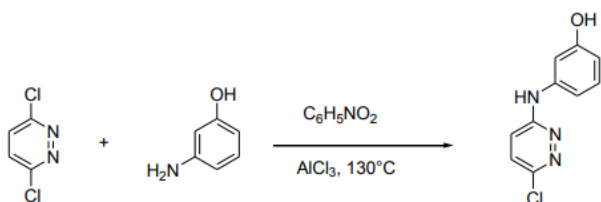


Figure 10: Arylation of 3,6-dichloropyridazine

v. Reaction with Oxidising and Reducing Agents: Due to an electron shortage in the ring, pyridazine is also immune to the attack of oxidising agents. However, when using hydrogen peroxide, N-oxide is formed but no di-N-oxide is produced. [11]

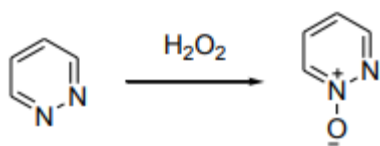


Figure 11: Reaction of pyridazine with hydrogen peroxide

Natural pyridazines

The chemistry of natural substances is a common source of lead structures. Very, there are surprisingly few natural chemicals that have the usual N-N bond seen in pyridazine molecules. Most of them are isolated from broths used to cultivate Streptomyces. The novel antifungal drug Pyridazomycin (Figure 12),

which is made by the bacteria Streptomyces violaceoniger sp. griseofucus, is the first known instance of totally unsaturated pyridazine occurring in nature. [12]

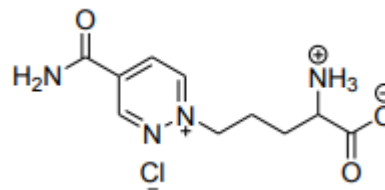


Figure 12: Pyridazomycin a natural antibiotic

Activity of pyridazine analogues biological

The phenyl moiety is included in the construction of around 50% of medicinal compounds. Many thousands of diazaequivalents are now accessible thanks to the substitution of these phenyl rings with pyridazines. Additional interaction opportunities are made possible by using pyridazine scaffolds rather than phenyl scaffolds. Pyridazine derivatives have been shown to have anti-cancer, antihypertensive, anti-allergic, anti-histaminic, eosinophil chemotaxis-inhibiting, anti-inflammatory, anti-PAF (platelet-activating factor) activity, anti-HIV activity, anti-histaminic, and similar properties. They are also useful as an agent for preventing or treating asthma, allergic rhinitis, allergic conjunctivitis. Credazine (Figure 13), pyridafol (Figure 14), pyridate (Figure 15), and maleic hydrazide are only a few herbicides that have the pyridazine structure (Figure 16). Several pharmaceutical medications, including cilazapril, cadralazine, minaprine, hydralazine, and cefozopran, also include pyridazine in their structural makeup (Figure 21). A magic moiety with a wide range of biological functions is pyridazine-3-one. NSAIDs with a pyridazine nucleus are being developed with more urgency. [13]

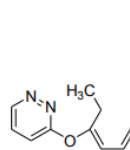


Figure 13: Credazine

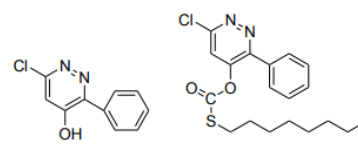


Figure 14: Pyridafol

Figure 15: Pyridate

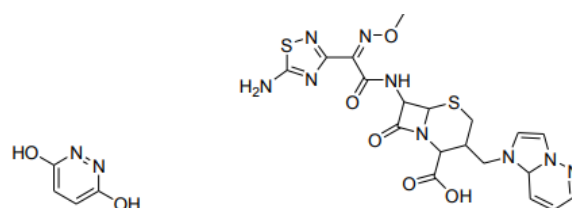


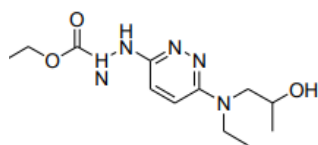
Figure 16: Maleic hydrazide
Cefozopram


Figure 17:

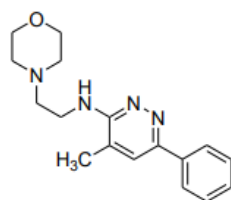


Figure 18: Cadralazine Figure 19: Minaprine

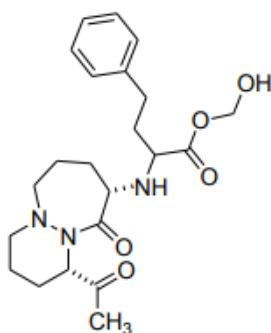
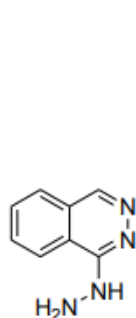


Figure 20: Hydralazine Figure 21: Cilazapril

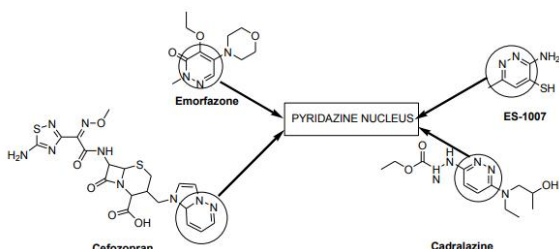


Figure 22: Pyridazine Nu2.

ANTI-INFLAMMATORY ACTIVITY

The biological reaction of vascular tissues to damaging stimuli, such as irritants, infections, or damaged bodily cells, is inflammation. If left untreated, inflammation triggers the development of conditions including atherosclerosis, rheumatoid arthritis, and vasomotor rhinorrhea. Proinflammatory cytokines including vascular endothelial growth factor (VEGF), interleukin 1L-1, and tumour necrosis factor (TNF)- are present throughout the dynamic process of inflammation. [14]

Multiple assays have been performed to compare the effectiveness of different NSAIDs; the findings show that the vast majority of these drugs are more effective against COX-1 than COX-2. Proven anti-inflammatory effects have been shown with MAP kinase inhibitors, glutathione S-transferase (GST) inhibitors, and inhibitors of nuclear factor kappa B

activation. Figure 23 provides a basic explanation of the NSAIDs' mode of action. [15]

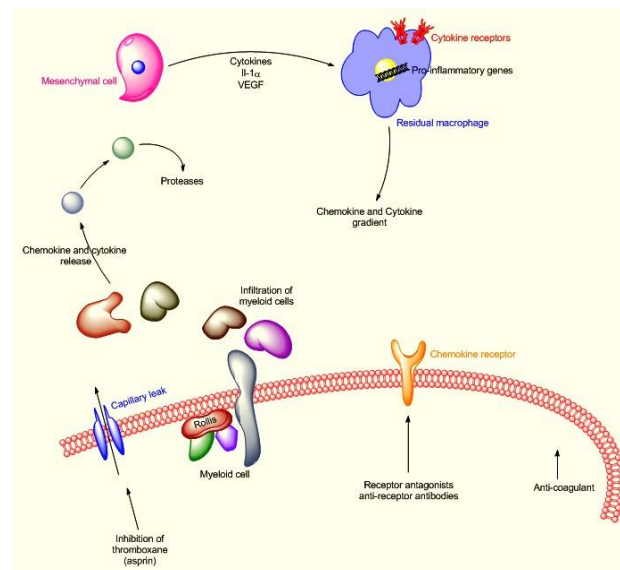


Figure 23: NSAIDs' mechanism of action

Antimicrobials

The development of novel, multi-resistant bacterial strains has been caused by the recent rise in antibiotic-resistant strains of clinically significant pathogens. There is a need to search for chemicals from other sources as a result. Because pyridazine results must be proven to have potent antibacterial and antifungal properties, they can serve as a source of novel antimicrobial chemicals. [16]

The term "antimicrobial" is used to describe a wide variety of substances used to kill germs. There is a wide range of antibacterial activity and mechanisms of action among them. Most of them exhibit distinctive pharmacological and physicochemical properties. Anti-infective drugs have been used for centuries to save many lives. Chemotherapy for bacterial infections is more common among anti-infectives than anti-fungal, antiviral, and antiparasitic treatments. Modern human society is largely the product of this knowledge. In 1910, Ehrlich developed the first successful antibiotic, Salvarsan (Figure 24). Since then, antibiotics from other classes, such as penicillins, sulphonamides, and beta-lactams, have shown the most promise. [17]

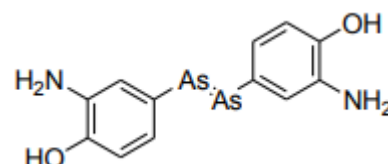


Figure 24: Structure of Salvarsan

antibiotics' various classes

The discovery of antibiotics as a means of curing bacterial illnesses is among the most important developments in medicine during the past half-century. There are other ways to classify antibiotics, but the most prevalent is based on their chemical structures. Antibiotics come in many forms; some of the most common include sulphonamides, oxazolidinones, and glycopeptides.. [18]

Antibiotic action mechanism

- Reduction in cell wall formation
- Impairment of cell membrane structure or function
- Blocking the formation and activity of nucleic acids
- protein synthesis inhibition
- Blockage of key metabolic pathways
- Disruption and increased permeability of cytoplasmic membranes

ANTIBIOTIC RESISTANCE AND NEED FOR NEW ANTIBIOTICS

Scientific intervention is needed to implement some control measures since resistance to antimicrobial drugs has been found to be a significant barrier to the clinical treatment and cure of many illnesses. There are just a few ways for microbes to develop antibiotic resistance. The most important survival methods that a threatened microbial population might utilise are genetic mutation, the appearance of a dormant resistance gene, and the acquisition of genes that contain resistance determinants. Some of the genes are inherited, while others appear as the result of chance changes in the DNA of microbes.[19]However, the discovery of bacterial antibiotic resistance calls into question the therapeutic utility of currently existing drugs and needs the creation of new antibacterial substances. The progressive chemistry-based augmentation of existing antibiotics is one example, and genomic-based searches for possible therapeutic targets are only two of the many ways that have arisen to uncover novel pharmacological targets. Finding new chemical compounds to study is essential for developing new medicines. This approach to drug discovery is explained with reference to drug design principles and recent developments in synthetic medicines or compounds. [20]

CONCLUSION

Finally, we can say that we effectively created new chemicals, 1, 2, and 3-trizole derivatives. Utilizing a CuAAC technique with ultrasound assistance, we have produced 1, 2, and 3-trizole derivatives in high yields. One-pot operation, easy work-up, good yields, shorter reaction time, and absence of column chromatographic purification are some of this reaction's key benefits. Antimicrobial properties against several strains of bacteria and fungus were tested for in all freshly synthesised compounds. As a consequence, certain synthetic substances demonstrated moderate to good antimicrobial efficacy against various types of bacteria and fungus when compared to traditional medications.

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