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MEDICINAL IMPORTANCE OF PYRAZOLO [3,4-D] PYRIMIDINE AND ITS DERIVATIVES: A REVIEW

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Review Paper

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ABSTRACT

Pyrazolo [3,4-d] pyrimidine, a fused heterocyclic compound, has attracted significant interest in medicinal chemistry due to its wide range of biological activities. This compound and its derivatives are valuable scaffolds in the development of therapeutics, especially for cancer, inflammation, infections, and various other diseases. The unique structure and versatility of pyrazolo [3,4-d] pyrimidine have led to the synthesis of numerous derivatives with enhanced biological activities. This review aims to provide an in-depth information of history, chemical properties, synthesis methods, and medical significance of pyrazolo [3,4-d] pyrimidine and its derivatives, highlighting their role in drug discovery and therapy.

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Keywords: Anticancer, Antituberculosis Medicinal properties, Pyrazolo [3,4-d] pyrimidine.

INTRODUCTION

Pyrazolo [3,4-d] pyrimidine is a bicyclic heterocyclic compound containing a fused pyrazole and pyrimidine ring system. This structure makes pyrazolo [3,4-d] pyrimidine an ideal candidate for the synthesis of bioactive molecules. Since 1970s, pyrazolo [3,4-d] pyrimidine (fig.1) derivatives have been investigated for their pharmacological potential in various therapeutic areas, including oncology, inflammation, and infectious diseases. Researchers have synthesized a wide array of derivatives, each with varying biological activities, broadening the scope of pyrazolo [3,4-d] pyrimidine in drug development.

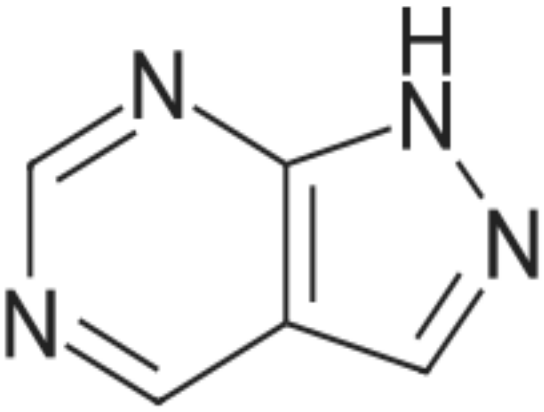

Fig. 1: Pyrazolo [3,4-d] pyrimidine.

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This review delves into the historical background, chemical properties, synthesis methods, and medical applications of pyrazolo [3,4-d] pyrimidine and its derivatives. It also explores how modifications to the pyrazolo [3,4-d] pyrimidine structure has enhanced its therapeutic potential.

HISTORICAL BACKGROUND

Pyrazolo [3,4-d] pyrimidine was first synthesized in the early 20th century, but its medicinal properties were not fully appreciated until the 1970s. Initial studies focused on its chemical structure and its interactions with other biological molecules. During the subsequent decades, researchers began to identify the compound's ability to inhibit various enzymes critical for cellular signalling, which opened the door to its use in drug discovery.

The early research on pyrazolo[3,4-d] pyrimidine focused on the synthesis of simpler derivatives, and over time, its potential for targeting key enzymes in cancer and inflammation pathways was recognized. These derivatives became central to the development of anticancer, anti-inflammatory, and antiviral therapies. Today, pyrazolo [3,4-d] pyrimidine and its derivatives remain the subject of intense investigation due to their broad spectrum of biological activity.

CHEMICAL STRUCTURE AND SYNTHESIS

The pyrazolo [3,4-d] pyrimidine core consists of two nitrogen-containing heterocyclic rings, pyrazole and pyrimidine, fused together. This structure not only contributes to its chemical stability but also enhances its ability to interact with various biological targets, such as kinases and enzymes involved in inflammation, cancer, and infection.

Synthesis Methods

Various synthetic routes have been developed for the preparation of pyrazolo [3,4-d]pyrimidine and its derivatives, including traditional condensation reactions, metal-catalysed reactions, and more recent approaches that use greener, sustainable methods. Some of the key methods for the synthesis of pyrazolo [3,4-d] pyrimidine derivatives are:

1. **Cyclization of Hydrazones:** A common approach involves the condensation of hydrazones with appropriate aldehydes or ketones to form pyrazolo [3,4-d] pyrimidine derivatives.
2. **Condensation Reactions:** The condensation of substituted pyrazole and pyrimidine precursors in the presence of acid or base catalysts yields pyrazolo [3,4-d] pyrimidine derivatives. These reactions are often carried out under mild conditions to improve yields and reduce by-products.
3. **Metal-catalyzed Reactions:** More recent synthetic strategies have introduced metal-catalyzed reactions, such as palladium or copper-catalyzed cyclizations, which allow for more selective and efficient formation of pyrazolo[3,4-d] pyrimidine derivatives. These methods are particularly useful for preparing derivatives with functional groups at specific positions on the core structure.
4. **Green Synthesis Methods:** With increasing concern for environmental impact, researchers are exploring sustainable synthetic strategies, including solvent-free reactions and the use of renewable resources.

MEDICINAL IMPORTANCE

The medical significance of pyrazolo[3,4-d] pyrimidine and its derivatives lie in their ability to modulate key biological targets. These compounds exhibit a variety of pharmacological properties, including anticancer, anti-inflammatory, antiviral, and antimicrobial effects. The following sections describe the therapeutic importance of these compounds in different disease areas:

1. Anticancer Activity

Cancer is a group of diseases involving abnormal cell growth with a potential to spread to other parts of the body (Verma, 2017; Masroor et al. 2020; Saha et al. 2020). Ruzi, Z *et al*. (2022) demonstrated that pyrazolo[3,4-d] pyrimidine derivatives act as potent inhibitors of kinases like c-ABL, which is involved in leukaemia and other cancers. These compounds showed promising results in inhibiting cancer cell growth.

2. Antiviral Activity

Some pyrazolo[3,4-d] pyrimidine derivatives have shown antiviral effects, particularly against viruses such as HIV reverse transcriptase and influenza (Jang *et al.*, (2009). These compounds have been found to inhibit viral replication by targeting viral enzymes such as reverse transcriptase or protease.

3. Antimicrobial Activity

Several pyrazolo[3,4-d] pyrimidine derivatives have exhibited significant antimicrobial properties particularly against Gram-positive bacteria, effective against a wide range of bacterial and fungal pathogens(Khobragade *et al.*, 2010).

4. Anti-inflammatory Activity
Pyrazolo[3,4-d] pyrimidine derivatives have been explored for their anti-inflammatory effects, as they can inhibit certain enzymes involved in the inflammatory process, such as cyclooxygenase (COX) involved in the production of pro-inflammatory prostaglandins(Rathore *et al*., 2016).

5. Neuroprotective Activity
Some pyrazolo[3,4-d] pyrimidine derivatives have shown neuroprotective effects and have been studied for their potential in treating neurodegenerative diseases such as Alzheimer's and Parkinson's diseases(Kim *et al*., 2013).

6. Antidiabetic Activity
Pyrazolo[3,4-d]pyrimidine derivatives have also been investigated for their antidiabetic effects, including the inhibition of enzymes involved in glucose metabolism such as α-glucosidase.(Li, Y., *et al*., 2018, Reddy *et al*. 2019)

7. Anticancer and Cell Cycle Arrest
Pyrazolo[3,4-d]pyrimidine derivatives have shown significant anticancer effects by modulating cell cycle progression and inducing apoptosis in various cancer cell lines. These compounds interact with multiple targets such as cyclin-dependent kinases (CDKs), which are crucial for the regulation of the cell cycle.(Zhou et al., 2017).

8. Inhibition of Protein Kinases
Protein kinases play a pivotal role in cancer progression, and pyrazolo[3,4-d] pyrimidine derivatives are known to inhibit various kinases, including serine/threonine kinases and tyrosine kinases, which are involved in signalling pathways that regulate cell proliferation and survival(Zhao *et al*., 2016).

9. Antichemotactic Activity
Some pyrazolo[3,4-d] pyrimidine derivatives have been shown to inhibit the migration and chemotaxis of immune cells, which can be useful for controlling inflammation and modulating immune responses(Li *et al*., 2018)

10. Antioxidant Activity
Some pyrazolo[3,4-d] pyrimidine derivatives demonstrate antioxidant properties, which may be beneficial in preventing oxidative stress-related diseases such as cardiovascular diseases, diabetes, and neurodegenerative conditions(Wang *et al*., 2014).

11. Antifungal Activity
Pyrazolo[3,4-d] pyrimidine derivatives have been shown to have antifungal properties, particularly against fungi that cause systemic infections, such as *Candida* species(Cheng *et al*., 2011).

12. Antituberculosis Activity
Given the rise in multidrug-resistant tuberculosis (MDR-TB), there is an increasing interest in finding novel compounds to treat this disease. Pyrazolo[3,4-d] pyrimidine derivatives have been evaluated for their potential in treating tuberculosis(Kumar *et al*., 2017).

13. Antidiabetic and Hypolipidemic Effects
In addition to their antidiabetic activity through enzyme inhibition, some pyrazolo[3,4-d]pyrimidine derivatives have demonstrated hypolipidemic effects, which help in lowering blood lipid levels, beneficial for patients with type 2 diabetes and hyperlipidemia (Amin *et al*., 2023).

14. Inhibition of α-Glucosidase and α-Amylase
Pyrazolo[3,4-d] pyrimidine derivatives have been shown to inhibit carbohydrate-hydrolyzing enzymes like α-glucosidase and α-amylase, which play a significant role in carbohydrate digestion and glucose absorption(Zhou et al., 2015).

15. Neuroinflammatory Activity
Neuroinflammation is a key component in various neurodegenerative diseases such as Alzheimer's and Parkinson's. Pyrazolo[3,4-d] pyrimidine derivatives have been shown to reduce neuroinflammation by inhibiting the activation of microglia and astrocytes, the primary cells involved in central nervous system (CNS) inflammation(Yang *et al*., 2019).

16. Inhibition of Monoamine Oxidase (MAO)
Pyrazolo[3,4-d] pyrimidine derivatives have been evaluated for their potential to inhibit monoamine oxidase (MAO), an enzyme responsible for the breakdown of neurotransmitters like dopamine and serotonin. Inhibition of MAO can have therapeutic implications for conditions like Parkinson's disease and depression(Kang *et al*., 2015).

17. Antiplatelet Activity
Pyrazolo[3,4-d] pyrimidine derivatives have been shown to exhibit antiplatelet effects by inhibiting platelet aggregation, which could potentially help in preventing thromboembolic diseases (Choi *et al*., 2013).

18. Anti-Alzheimer's Activity
The accumulation of amyloid plaques and the dysfunction of acetylcholinesterase (AChE) are key features in Alzheimer's disease. Pyrazolo[3,4-d] pyrimidine derivatives have been investigated for their potential to inhibit AChE and reduce amyloid aggregation, making them promising candidates for treating Alzheimer's disease(Singh *et al*., 2017).

19. Antihypertensive Activity
Pyrazolo[3,4-d] pyrimidine derivatives have also been shown to possess antihypertensive properties, potentially through their ability to regulate the renin-angiotensin system or inhibit vasoconstriction.(Patel *et al*., 2018).

20. Inhibition of Histone Deacetylases (HDAC)
Histone deacetylases (HDACs) are enzymes that regulate gene expression and are involved in many diseases, including cancer. Pyrazolo[3,4-d] pyrimidine derivatives have been studied for their potential to inhibit HDACs, leading to the re-expression of tumour suppressor genes and the inhibition of cancer cell growth(Hernandez *et al*., 2019).

21. Antioxidant and Anti-Aging Properties
Pyrazolo[3,4-d] pyrimidine derivatives have been shown to have antioxidant activity, which can help mitigate oxidative stress and potentially delay the aging process by protecting cellular structures from free radical damage(Chen *et al*., 2016).

22. Antidiarrheal Activity
Some pyrazolo[3,4-d] pyrimidine derivatives have shown antidiarrheal effects, likely by modulating gastrointestinal motility or by inhibiting secretory processes in the gut(Sadeghi *et al*., 2017).

23. Antispasmodic Activity
Some pyrazolo[3,4-d] pyrimidine derivatives have shown antispasmodic effects by relaxing smooth muscle tissues, which can be useful in treating conditions like irritable bowel syndrome (IBS) or other gastrointestinal disorders(Patel *et al.,* 2015).

24. Anticystic Fibrosis Activity
Pyrazolo[3,4-d] pyrimidine derivatives have been investigated for their potential to treat cystic fibrosis (CF), a genetic disorder affecting the lungs and digestive system. These compounds may act by modulating the CFTR (cystic fibrosis transmembrane conductance regulator) protein function.(Simpson *et al*., 2014).

25. Anti-Obesity Activity
Obesity is a nutritional disorder that spans all ages, ethnicities and affects both the sexes (Verma, 2017; Saba, and Balwan, 2025). Some pyrazolo[3,4-d] pyrimidine derivatives have demonstrated the potential to combat obesity. This effect is generally mediated through the regulation of adipogenesis, lipid metabolism, and food intake, potentially targeting key proteins such as peroxisome proliferator-activated receptors (PPARs)(Hwang *et al*. 2019).

26. Inhibition of HIV Integrase
Pyrazolo[3,4-d] pyrimidine derivatives have been studied for their ability to inhibit HIV integrase, an enzyme essential for the integration of viral DNA into the host genome. By blocking this step, these compounds could contribute to the development of novel HIV treatments(Patil *et a*l., 2017).

27. Antimelanoma Activity
Pyrazolo[3,4-d]pyrimidine derivatives have been explored for their potential in treating melanoma, a form of skin cancer. These compounds have shown promising results in inhibiting melanoma cell proliferation and inducing apoptosis (Xie *et al.,* 2016).

28. Inhibition of Tumor Necrosis Factor-alpha (TNF-α) Production
Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine involved in various inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease (IBD). Pyrazolo[3,4-d] pyrimidine derivatives have been shown to inhibit TNF-α production, suggesting their potential as anti-inflammatory agents(Zhou *et al.,* 2014).

29. Antileishmanial Activity
Pyrazolo[3,4-d] pyrimidine derivatives have shown efficacy against *Leishmania* species, which cause leishmaniasis, a neglected tropical disease. Some derivatives exhibit inhibitory activity against the enzymes necessary for parasite survival(Jain *et al*., 2016).

30. Anti-Angiogenic Activity
Angiogenesis, the formation of new blood vessels, is critical for tumor growth and metastasis. Pyrazolo [3,4-d] pyrimidine derivatives have been shown to inhibit angiogenesis, making them potential candidates for cancer therapy(Abdelhamed *et al*., 2023).

31. Inhibition of Microtubule Dynamics
Some pyrazolo[3,4-d] pyrimidine derivatives interact

with microtubules, which are essential for cell division. These compounds can inhibit microtubule polymerization and disrupt the mitotic spindle, leading to cancer cell death(Liu *et al.*, 2017).

32. Modulation of Immune Responses
Some pyrazolo[3,4-d] pyrimidine derivatives have shown the ability to modulate immune responses by influencing the activity of immune cells such as T cells, B cells, and dendritic cells. These compounds could be useful in immune-related disorders, including autoimmune diseases (Sharma *et al.*, 2015)

33. Inhibition of Aldose Reductase
Aldose reductase is an enzyme involved in the development of diabetic complications, including cataracts and neuropathy. Pyrazolo[3,4-d] pyrimidine derivatives have shown potential in inhibiting aldose reductase, offering a potential therapeutic approach for managing diabetes-related complications (Chaudhary *et al.*, 2019).

34. Antihyperlipidemic Activity
Pyrazolo[3,4-d] pyrimidine derivatives have demonstrated activity in lowering lipid levels, particularly in reducing cholesterol and triglyceride concentrations. This makes them useful in treating hyperlipidemia and related conditions, such as atherosclerosis (Gupta *et al*. 2016).

35. Anti-Mycobacterial Activity
Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), remains a global health challenge. Pyrazolo[3,4-d] pyrimidine derivatives have been investigated for their potential to inhibit mycobacterial growth, offering a pathway for developing new anti-TB agents(Zhou *et al.*, 2018).

36. Antiviral Activity (HCV)
Hepatitis C virus (HCV) remains a leading cause of liver disease worldwide. Pyrazolo[3,4-d] pyrimidine derivatives have been studied for their ability to inhibit HCV replication, providing a potential avenue for antiviral drug development(Wu *et al.*, 2017).

37. Inhibition of Protein Kinase C (PKC)
Protein kinase C (PKC) plays a pivotal role in cell signaling and is implicated in various diseases, including cancer and diabetes. Pyrazolo[3,4-d]pyrimidine derivatives have shown inhibitory effects on PKC, suggesting potential for treating related conditions (Kumar *et al.* 2019).

38. Antioxidant Properties
Pyrazolo[3,4-d]pyrimidine derivatives have been shown to possess antioxidant properties, which could play a role in reducing oxidative stress. These properties may be valuable for preventing diseases related to oxidative damage, such as neuro-degenerative disorders and cardiovascular diseases(Li *et al.*, 2017).

39. Anticancer Activity via Inhibition of JAK/STAT Pathway
The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a crucial role in cancer cell survival and proliferation. Pyrazolo[3,4-d]pyrimidine derivatives have been shown to modulate this pathway, making them potential candidates for cancer therapy (Zhao *et al.*, 2018).

40. Anti-Candidal Activity
Candidiasis, caused by *Candida* species, is a common fungal infection. Pyrazolo[3,4-d] pyrimidine derivatives have shown activity against *Candida* species, offering potential for antifungal drug development (Singh *et al.*, 2018).

41. Antidiabetic Activity via α-Glucosidase Inhibition
α-Glucosidase is an enzyme involved in the breakdown of carbohydrates to glucose. Inhibition of this enzyme can help manage blood glucose levels, making pyrazolo[3,4-d]pyrimidine derivatives potential candidates for the treatment of type 2 diabetes(Nayak *et al*. 2017).

42. Antimicrobial Activity Against Gram-Positive and Gram-Negative Bacteria
Pyrazolo[3,4-d] pyrimidine derivatives have exhibited broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, making them candidates for combating bacterial infections(Jang *et al.*, 2018).

43. Antihyperglycemic and Insulin Sensitizing Effects
Pyrazolo[3,4-d] pyrimidine derivatives have shown antihyperglycemic effects by enhancing insulin sensitivity, which is beneficial for managing insulin resistance and type 2 diabetes(Kim *et al.*, 2019).

44. Inhibition of DNA Topoisomerase
DNA topoisomerase enzymes are involved in the unwinding and rewinding of DNA during replication

and transcription. Inhibition of these enzymes can lead to cell death, especially in cancer cells. Pyrazolo[3,4-d] pyrimidine derivatives have been found to inhibit these enzymes, making them potential chemotherapeutic agents(Liu *et al*., 2017).

CONCLUSION

Pyrazolo[3,4-d] pyrimidine and its derivatives are of immense value in medicinal chemistry, with promising applications in the treatment of cancer, inflammation, infectious diseases, and other pathologies. The ability of these compounds to interact with a wide variety of biological targets, including kinases, enzymes, and receptors, makes them versatile candidates for drug development. As research progresses, new derivatives are likely to emerge, offering more potent and selective therapeutic options for treating diseases that have long been challenging to manage. The ongoing exploration of pyrazolo[3,4-d] pyrimidine derivatives continue to shape the future of pharmaceutical development, offering hope for the next generation of targeted therapies.

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