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

Pyrimidine-Based Compounds: Synthesis and Therapeutic Applications

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ABSTRACT:

Nitrogen containing synthetically and biologically important heterocyclic ring system namely pyrimidine possess both biological and pharmacological activities and defend as aromatic six heterocyclic with 1 and 3 nitrogen atom in ring. Preparation of pyrimidine via different methods offer its importance in fields of medicinal chemistry and chemistry. Pyrimidines and their derivatives act as anti-inflammatory, anti-malaria, anti-tumor. cardiovascular agents, anti-neoplastic. anti-tubercular, anti-HIV, diuretic, anti-viral, anti-microbial, analgesic. This review give light up on biological and pharmacological activities of pyrimidine nucleus.

KEYWORDS:
Antioxidant. Antimicrobial. Antibacterial, Antifungal, Antiviral, Pyrimidine derivatives.

INTRODUCTION:

Pyrimidine, an aromatic heterocycle, contains two nitrogen atoms in the ring at 1st and 3rd positions. In 1984 Pinner studied pyrimidines systematically by synthesizing derivatives through condensation of ethyl acetoacetate with amidines and first proposed the name “pyrimidin” in 1885. In 1900 Gabriel and Colman synthesized 2,4,6-trichloropyrimidine from barbituric acid which was then reduced by zinc dust in hot water to give the parent compound(2).

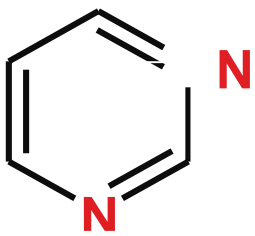


Figure No 1. Pyrimidine structure

Pyrimidine is an imperative heterocyclic ring, and as a part of various pharmacophores, it presents a diverse spectrum of biological activities making valuable in medicinal chemistry. As a result, there is a never-ending hunt for an environmentally sustainable method of its synthesis. Pyrimidine derivatives are a class of heterocyclic compounds that have been widely studied for their diverse pharmacological activities(1). These compounds have been found to exhibit antimicrobial, anti-inflammatory, antioxidant, and anticancer properties, making them potential candidates for the development of new drugs.

Biological significance of pyrimidine is:

Pyrimidines are essential building blocks of life with diverse biological roles. They are found in:

1. Nucleic Acids: Cytosine, thymine, and uracil are pyrimidines that form the core of

DNA and RNA, carrying genetic information.

2. Vitamins: Thiamine (Vitamin B1) contains a pyrimidine ring and is crucial for energy metabolism.

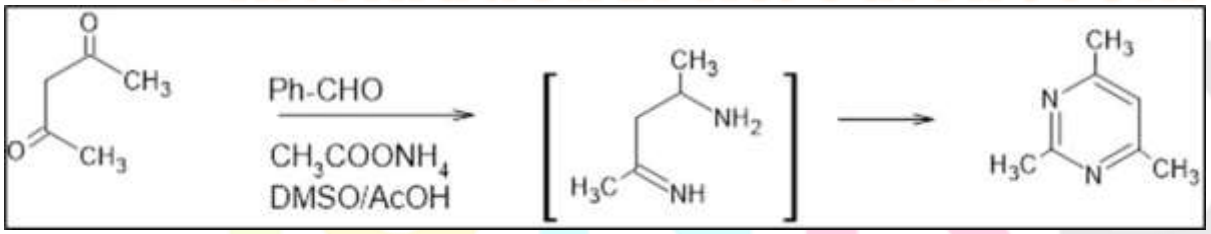
3. Coenzymes: Pyrimidine nucleotides are involved in various enzymatic reactions and cellular processes.

Chemical synthesis of pyrimidine derivatives

- **From Acetyl Acetone**

Reacting benzaldehyde and acetyl acetone in the presence of two equivalents of ammonium acetate, which produced the intermediate (Z)-4-iminopent-2-en-2-amine.

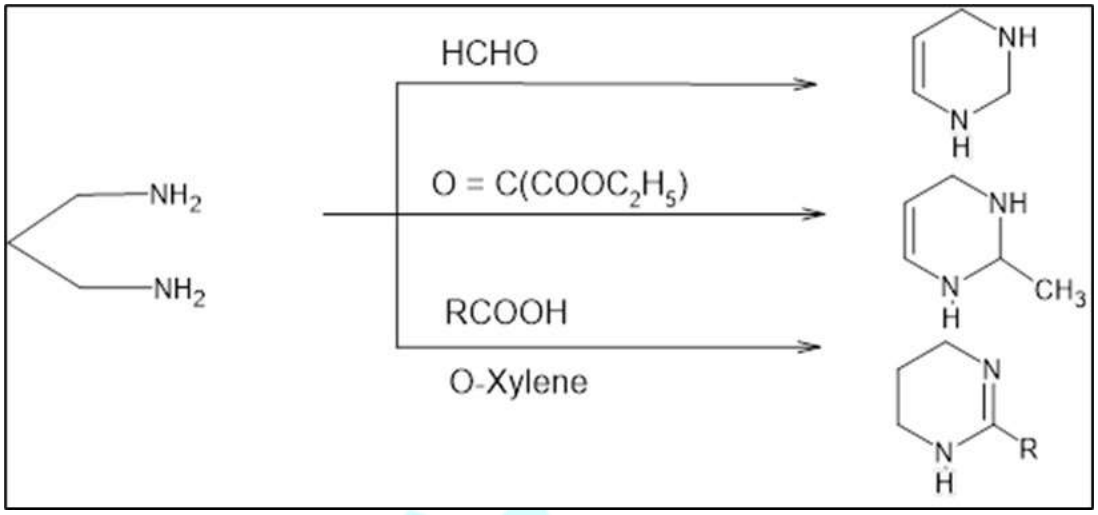
From there, a process produced the primidine derivative(3).



Scheme 1 Synthesis of pyrimidine derivatives from acetyl acetone

- **From 1,3-diaminopropane**

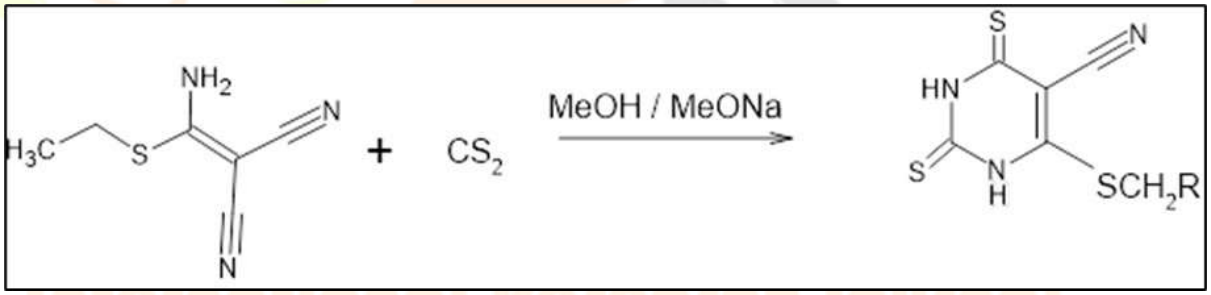
reacting 1,3-diaminopropane with formaldehyde, diethyl carbonate, and carboxylic acid to produce the corresponding pyrimidine derivatives(5).



Scheme 2 Synthesis of pyrimidine derivatives from 1,3-diaminopropane

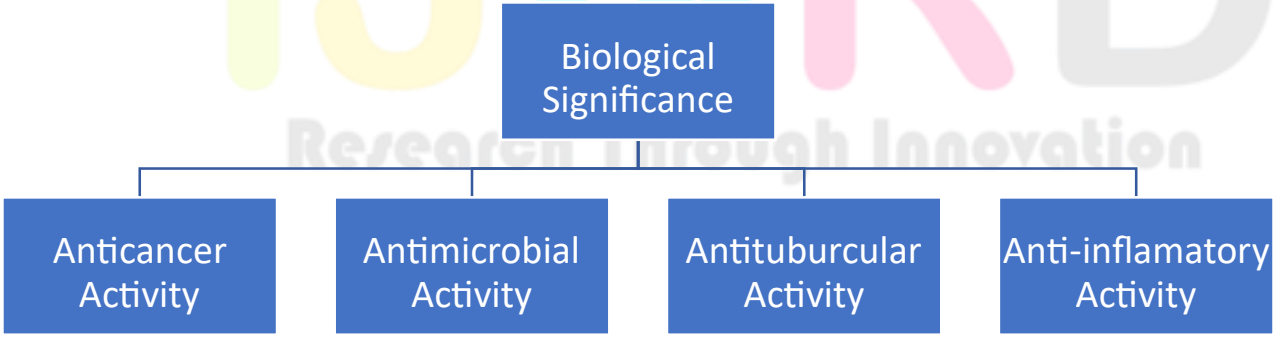
- **From Enaminonitrile**

By using CS2 on enaminonitrile (10) in the presence of sodium methoxide, they were able to produce pyrimidinethione derivative(6).



Scheme 3 Synthesis of pyrimidine derivative from enaminonitrile

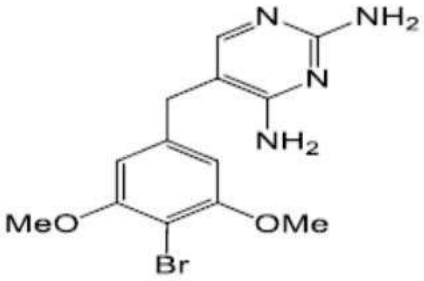
Biological Significance:



Antimicrobial Activity

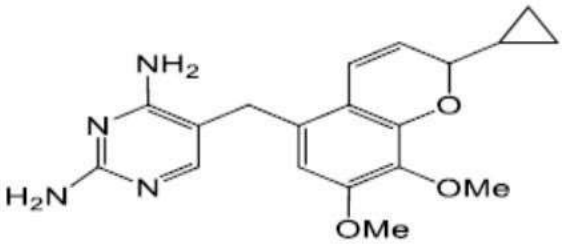
Pyrimidine-based antifolates and sulfa drugs demonstrate significant antimicrobial properties. Notable examples include Brodiprim (1) and Iclaprim (2), which exhibit potent antibacterial activity through selective

dihydrofolate reductase inhibition. Trimethoprim (3) shows selective bacterial DHFR inhibition, while Pyrimethamine (4) targets malarial plasmodia



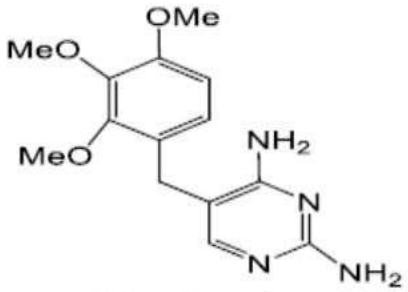
Brodiprim

(1)



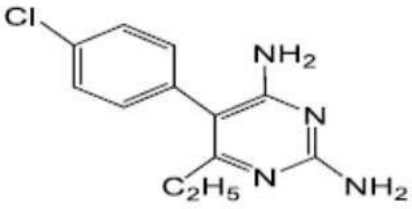
Iclaprim

(2)



Trimethoprim

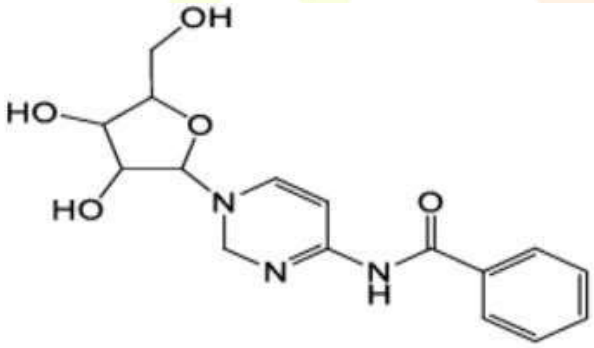
(3)



Pyrimethamine

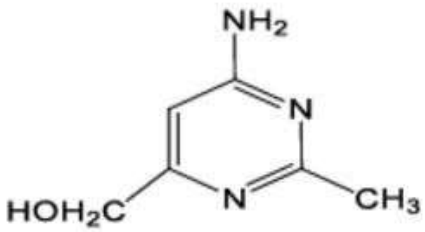
(4)

Antibiotic compounds containing pyrimidine moieties include Amicetine (5), Bacimethrin (6), and Bleomycin



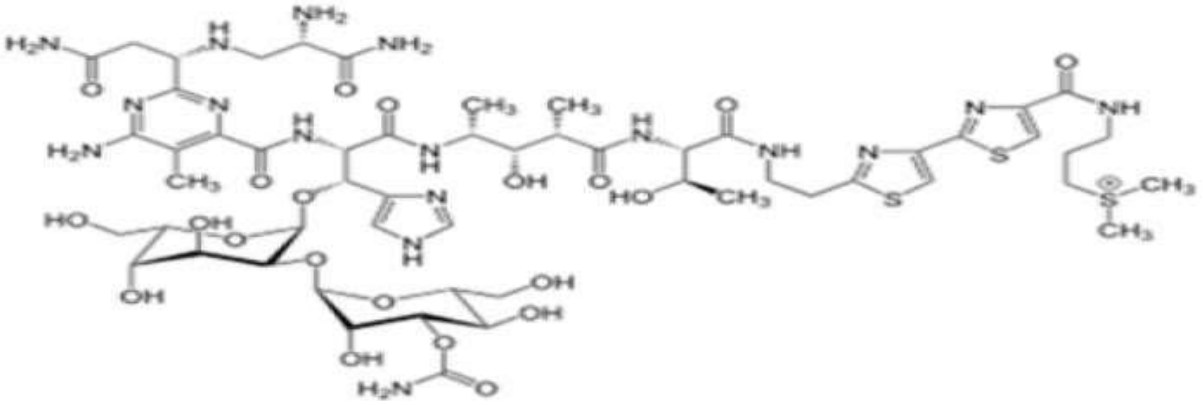
Amicetin

(5)



Bacimethrin

(6)

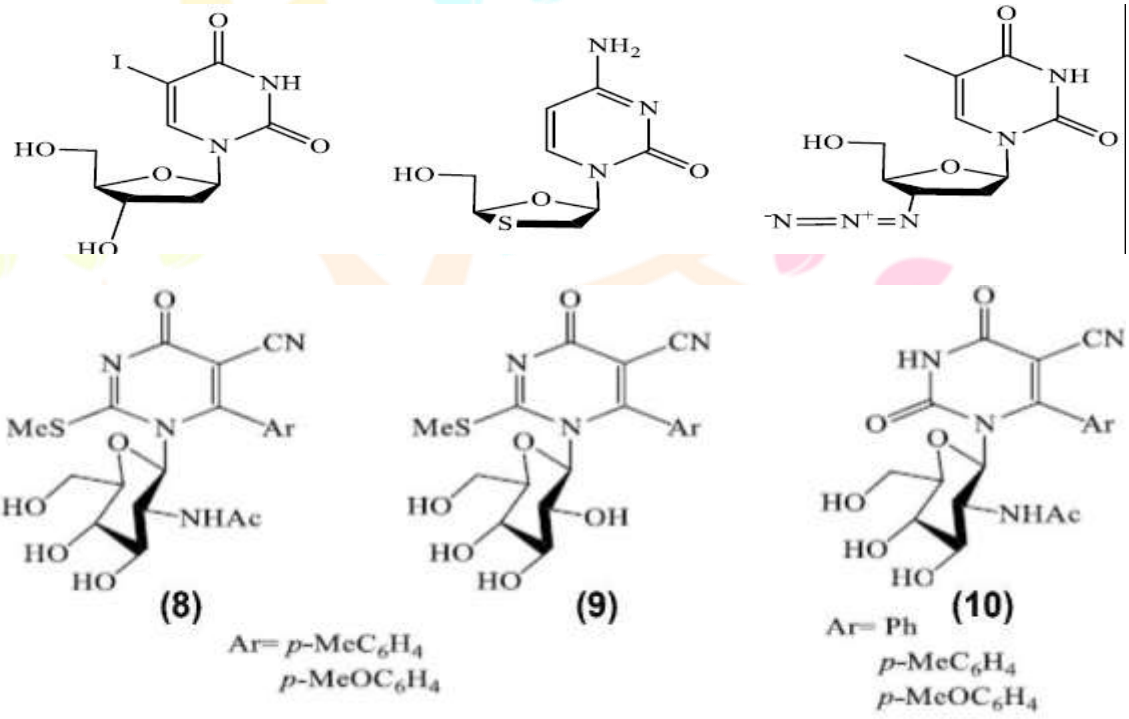


Bleomycin (7)

Antiviral Activity

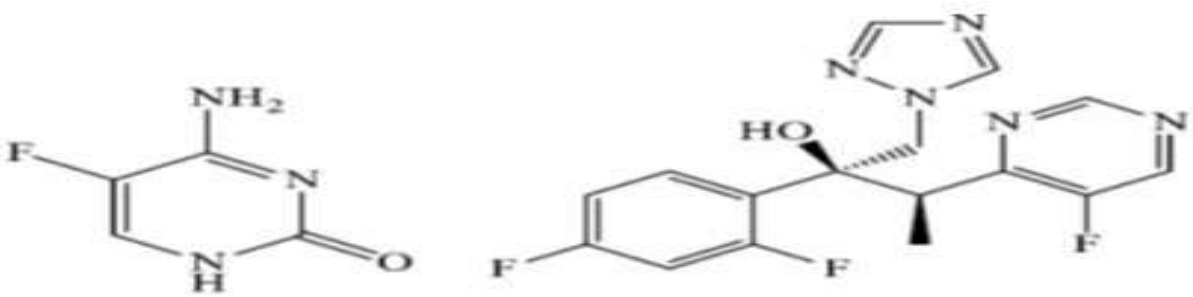
Pyrimidine derivatives exhibit significant antiviral properties through various mechanisms. The nucleoside analog 5-iododeoxyuridine demonstrates broad-spectrum antiviral activity. Lamivudine, particularly effective against HIV when combined with Zidovudine, represents a crucial advancement in antiretroviral therapy. Zidovudine, a thymidine analog, shows specific activity against RNA tumor viruses through its interaction with viral reverse transcriptase [28].

Novel pyrimidine glycoside derivatives (8-10) have shown promising activity against HBV in HepG2.2.2.15 cell lines. These compounds demonstrate moderate viral replication inhibition while maintaining acceptable cytotoxicity profiles(8).



Antifungal Activity

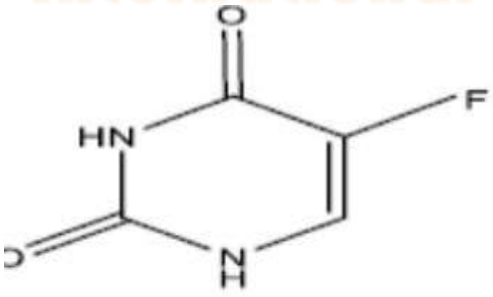
Pyrimidines also exhibit antifungal properties, Flucytosine is a fluorinated pyrimidine and is an orally active antifungal agent, which is used for the treatment of serious systemic infections caused by susceptible strains of Candida Cryptococcus also Voriconazol is a disubstituted drug used a s a broad spectrum antifungal agent.



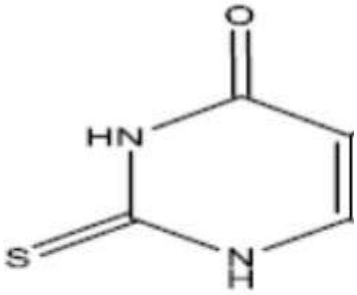
Drug Name	Chemical Class	Therapeutic Category	Mechanism of Action
Trimethoprim	Diaminopyrimidine	Antibacterial	DHFR inhibitor
Zidovudine	Nucleoside analog	Antiviral	Reverse transcriptase inhibitor
5-Fluorouracil	Pyrimidine analog	Anticancer	Thymidylate synthase inhibitor
Lamotrigine	Aminopyrimidine	Anticonvulsant	Na+ channel blocker
Rosuvastatin	Pyrimidine derivative	Antihyperlipidemic	HMG-CoA reductase inhibitor
Imatinib	Pyrimidine derivative	Anticancer	Tyrosine kinase inhibitor
Raltegravir	Pyrimidine derivative	Antiviral	HIV integrase inhibitor

Antineoplastic Activity

Pyrimidine-based compounds play a crucial role in cancer therapy. 5-Fluorouracil and its derivatives function as antimetabolites, interfering with nucleic acid synthesis in rapidly dividing cells. Modified pyrimidine nucleosides exhibit significant activity against various tumor cell lines through multiple mechanisms, including DNA synthesis inhibition and cell cycle regulation.



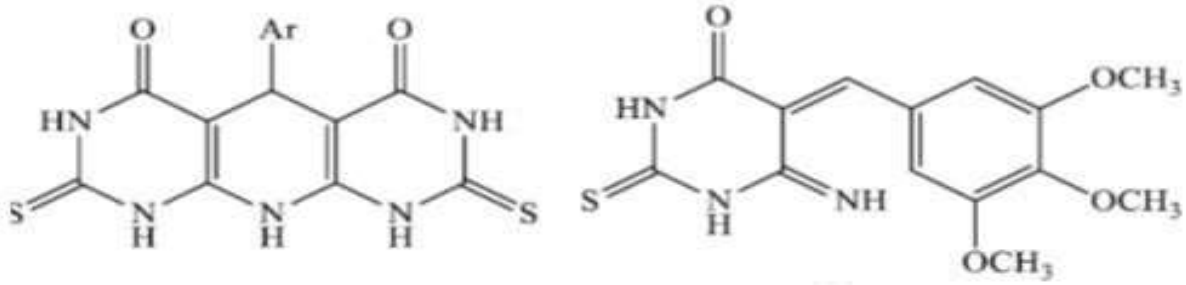
5-Fluorouracil



2-Thiouracil

Anti-inflammatory Activity

Several pyrimidine derivatives demonstrate potent anti-inflammatory properties. These compounds modulate inflammatory mediators and exhibit COX-2 inhibitory activity. Structure-activity relationship studies have revealed that specific substitution patterns on the pyrimidine ring enhance anti-inflammatory efficacy while reducing adverse effects



Antihypertensive Activity

Pyrimidine-containing compounds have emerged as effective antihypertensive agents. These derivatives act through various mechanisms, including calcium channel blockade and angiotensin receptor modulation. The incorporation of specific functional groups enhances their binding affinity to relevant therapeutic targets.

Anthelmintic Activity

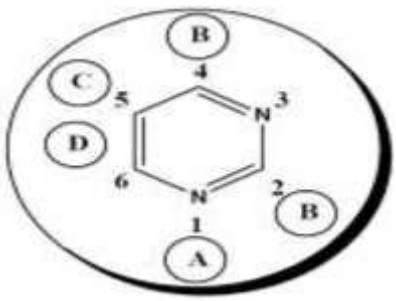
Modified pyrimidine scaffolds show promising anthelmintic properties. These compounds demonstrate efficacy against various parasitic infections through mechanisms involving disruption of parasitic cellular processes. Structure optimization has led to derivatives with improved potency and reduced host toxicity

Anti-hyperlipidemic Activity

Pyrimidine-based compounds effectively regulate lipid metabolism. These derivatives influence various aspects of lipid homeostasis, including cholesterol synthesis and lipoprotein metabolism. Recent developments have focused on enhancing their selectivity and reducing side effects.

Structure Activity Relationships (SAR) study

As SAR studies give insights into the molecular properties causing receptor affinity and selectivity. The promising nature of the compounds may be attributed to the substitutions at the hydrophobic domain. These compounds had electron withdrawing and donating groups at the orti, meta & para position of the hydrophobic aryl ring. In general it was observed that the substituted derivatives were more active than the other derivatives. This may be because of the fact that the substituted derivatives are better fitted into the receptor site. In all of the pioneering experiments important core fragments is defined by presence of hydrogen donor/acceptor unit (HAD), hydrophobic domain (A). (aryl ring substituted/unsubstituted) and electron donor atom (D). This common features was found in the structures of wellestablished pyrimidine drugs.



A. Five membered saturated heterocyclic ring substitution leads to anticancer and antiviral activities

B. 2th position six or five membered saturated heterocyclic ring substitution leads to anthelmintic, antiparkinsonisu expectorant and treatment of Gl disturbance, peripheral neuropathies

C. 2nd and 4th position keto group substitution or amino substitution or mixed keto, amino groups substitution leads to anticancer, antiviral, antibacterial, antifungal, and treatment of respiratory tract infection and liver disorder

D. 5th position with halogen or substituted amine or saturated distal heterocyclic ring substitution leads to antibacterial and anticancer activities

E. 5th and 6th position fused with heterocyclic ring and o, m, p substituted distal aryl ring substitution leads to anticancer, antiviral, antibacterial, vasodilation and treatment of urinary tract infection.

RESULT AND DISCUSSION:

This study highlights the diverse applications of pyrimidine derivatives in drug research and treatment. It is evident from this review that pyrimidine derivatives have been investigated for a number of diseases. Even so, pyrimidine and its derivatives are thought to possess a wide range of pharmacological properties, such as antibacterial, anticancer, antiinflammatory, and antitubarcular properties. The pharmaceutical industry greatly benefits from this chemical.

However, there are several barriers to developing new pyrimidine derivatives, including the need for better selectivity, reduced toxicity, and a deeper understanding of pharmacokinetic properties. All things considered, the state of this field's research holds promise for the creation of novel, effective treatments for a range of diseases. There is still room for more investigation in this field in the hopes of finding a novel pharmacological action. Additionally, because current medications are no longer effective, there is an urgent need for new research on pyrimidine derivatives.

AKNOWLEDGMENT:

We appreciate and extend our sincere gratitude to Prof. Dr. Lokhande, R.P., who made the work possible. His direction and counsel saw me through the entire paper-writing process. We also like to express our gratitude to our institute for providing us with this review article opportunity.

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