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Pharmacological Activities of Pyrimidine Derivatives: An Overview

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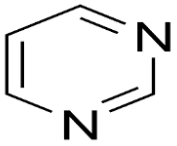
ABSTRACT: The present review article highlights the therapeutic potentials of pyrimidine derivatives, which are valuable for medical applications in the new generation. Heterocyclic compounds, including pyrimidine, offer a wide range of structural diversity and have demonstrated significant usefulness as therapeutic agents. Pyrimidine is compound that is similar to pyridine aromatic heterocyclic and is one of the three diazines. Extensive research has shown that heterocyclic pyrimidine derivatives play crucial roles in the pathophysiology of various diseases. The pyrimidine nucleus, a fundamental component of DNA, has been found to exhibit diverse biological activities. These include antimicrobial, anticancer, anti-inflammatory, antidiabetic, and analgesic activities. This review article aims to provide an overview of the reported work on the therapeutic potentials of pyrimidine derivatives, highlighting their significance in medical applications for the new generation.

Keywords: Pyrimidine, pyrimidine derivatives, pyrimidine nucleus, Pharmaceutical, Antimicrobial, Antiviral.

INTRODUCTION

Pyrimidine-based compounds exhibit diverse biological activities, showcasing their potential in various therapeutic areas. Notably, several examples highlight the efficacy of such compounds in the treatment of specific diseases. For instance, 5-fluorouracil demonstrates anticancer properties, while idoxuridine and trifluoridine serve as effective antiviral drugs. In the realm of HIV treatment, zidovudine and stavudine exhibit anti-HIV activity. Additionally, the antibacterial spectrum is not left untouched, with trimethoprim, sulphamethiazine, and sulfadiazine demonstrating efficacy against bacterial infections. These examples highlight the potential of pyrimidine derivatives to treat an extensive range of diseases and infections, as well as their versatility in drug development. Minoxidil and prazosin are antihypertensive drugs, and sulphadoxin is antimalarial and antibacterial. Barbiturates, like phenobarbitone, are used as tranquilizers, hypnotics, and anti-convulsants. The anti-thyroid drug propylthiouracil. The pyrimidine core is present in many naturally occurring and structurally complex synthetic derivatives, and as a result, it has garnered considerable attention. Due to their extraordinary pharmacological efficacy, pyrimidine derivatives have been the subject of an in-depth investigation into their biological role in the nucleus (Selvam *et al*., 2015; Mohana and Sompalle 2016).

Pyrimidine is similar to pyridine aromatic heterocyclic organic compound. It is a diazine and one of three such compounds (heterocyclics with six members and two nitrogen atoms in the ring) (Miller, 1995; Moradivalikboni *et al*., 2015a,b; Tiwari & Singh 2009). Other diazines include pyrazine (containing nitrogen 1 and 4) and pyridazine (containing nitrogen 1 and 2). The pyrimidines (or "m diazine") were recognized as byproducts of uric acid metabolism. Brugnateli isolated the first pyrimidine derivative, alloxan, in 1818. Pinner (Amir *et al*., 2007) first used the term pyrimidine, a portmanteau of the words pyridine and amidine.



Pyrimidine

Several pyrimidines (thymine, uracil, and cytosine) are produced during the hydrolysis of nucleic acids. Cytosine can be found in both DNA and RNA, while uracil is exclusive to RNA, and thymine is DNA (Cox, 1968).

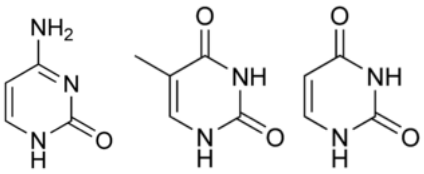
Physical Properties:

Molecular formula	$C_4H_4N_2$
Molar mass	80.088 g mol^{-1}
Density	1.016 g cm^{-3}
Melting point	20 °C (68 °F; 293 K)
Boiling point	123 °C (253 °F; 396 K)
Acidity (pK_a)	1.10 (protonated pyrimidine)

The electron density of pyrimidines is even lower than that of pyridines. Nucleophilic aromatic substitution becomes easier than electrophilic aromatic substitution becomes more difficult as a result. The amino group being removed from 2-aminopyrimidine by chlorine

and its subsequent reverse is an example of the last reaction type (Jain and Sharnevas 2008).

Pyrimidine derivatives are found in nucleic acid (Naik and Chikhalia, 2007) are thymine (T), Cytosine (C) and uracil (U)



Cytosine Thymine Uracil

Hydrogen bonds are formed between these bases and their complementary purines in DNA and RNA. Thus, the purines guanine (G) and adenine (A) pair up with the pyrimidines cytosine (C) and thymine (T) in DNA. In RNA, the complement of adenine (A) is uracil (U) rather than thymine (T), so the pairs that form are adenine: uracil and guanine: cytosine. In DNA, thymine or uracil can appear (Aly, 2005).

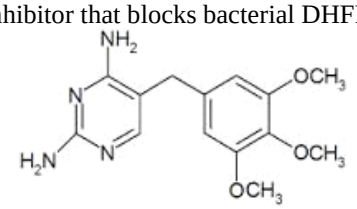
PHARMACEUTICAL ACTIVITIES

A. Antimicrobial Activity

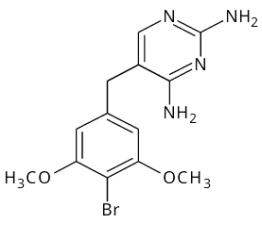
Microbial infections encompass a wide range of illnesses, including pneumonia, amoebiasis, typhoid, malaria, the common cold, flu, tuberculosis, influenza, syphilis, and AIDS. Over the years, extensive research has been conducted to explore the antimicrobial properties of the pyrimidine moiety.

Notably, in 1948, Hitchings discovered that several 2,4-diaminopyrimidines and certain 2-amino-4-hydroxypyrimidines act as antagonists for folic acid. Subsequently, it was revealed that these pyrimidines effectively inhibit dihydrofolate reductase (DHFR). Among the class of drugs known as 2,4-diaminopyrimidines, pyrimethamine stands out as a selective inhibitor of malarial plasmodia's DHFR. These findings contribute to our understanding of the antimicrobial potential of pyrimidine derivatives, particularly in targeting specific microbial enzymes and providing valuable insights for drug development (Russo *et al.*, 1999).

Trimethoprim is an antibacterial compound and selective inhibitor that blocks bacterial DHFR.



Trimethoprim



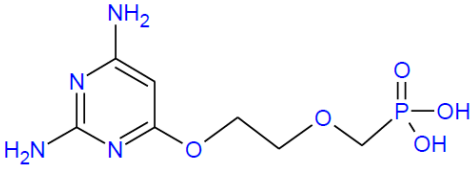
BRODIPRIM

Brodimoprim has been well-documented for its significant antibacterial properties. Moreover, pyrimidine compounds have demonstrated remarkable effectiveness as anti-fungal agents. Specifically, in the management of severe systemic infections caused by bacterial strains of Candida and Cryptococcus. flucytosine, a fluorinated pyrimidine, serves as a potent nucleosidal anti-fungal agent. Its utilization in such cases highlights its clinical efficacy in combating these life-threatening fungal infections (Cenicola *et al.*, 1990).

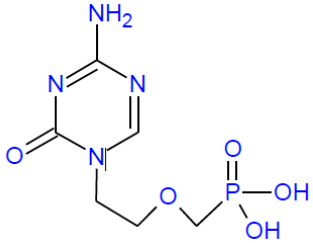
B. Anti-Viral Activity

Acyclic nucleoside phosphonates (ANPs) represent a significant class of compounds with diverse biological activities, primarily known for their potent antiviral effects. With the emergence of the pandemic caused by SARS-CoV-2, the importance of research and development of new antivirals has been highly evident.

In a study by Krecmerova *et al.* (2017) novel derivatives of 2,4-diamino-6-[2-(phosphonomethoxy) ethoxy]pyrimidines (PMEO-DAPy) and 1-[2-(phosphonomethoxy)ethyl]pyrimidines (PMEO-DAPy)-5-azacytosine (PME-5-azaC) were synthesized. These derivatives included various modifications such as carbonyloxymethyl esters (POM, POC), alkoxy alkyl esters, amino acid phosphoramidates, and/or a tyrosine pro-moiety, serving as prodrugs. The researchers investigated the *in vitro* antiviral efficacy of these prodrugs against multiple virus families, assessing their ability to inhibit viral replication and spread. By exploring the effectiveness of these ANP prodrugs against a broad range of viruses, this study sheds light on their potential as versatile antiviral agents with promising therapeutic applications (Krecmerova *et al.*, 2017).



Structure of 2,4-diamino-6-[2-(phosphonomethoxy)ethoxy]pyrimidine



Structure of 1-[2-(phosphonomethoxy)ethyl]-5-azacytosine

Similarly, Hisaki *et al.* (1999) research focuses on the efficient synthesis of 2-amino-4-(-hydroxyalkylamino)pyrimidine derivatives and their potential as anti-influenza virus agents. The study looks at how different substitutions affect the antiviral activity of these compounds. The results show that introducing cyclobutyl and cyclopentyl groups to the

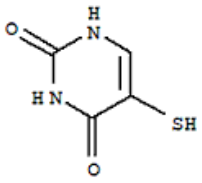
aminoalkyl group's -position, especially when substituted by a phenylalkyl group at the 3'-position, significantly increases their antiviral potency against influenza virus types A and B. Furthermore, the study reveals the relative importance of different pyrimidine ring substituents in determining antiviral efficacy. The compounds show promising antiviral indices, implying that they could be used in topical treatments for influenza virus infections (Hisaki *et al.*, 1999).

In an another example targeting influenza virus, Krasnov *et al.* (2022) investigated the synthesis and evaluation of pyrimidine conjugates containing a fragment of racemic 7,8-difluoro-3,4-dihydro-3-methyl-2H-[1,4]benzoxazine and its (S)-enantiomer. Various chloropyrimidines were used in nucleophilic substitution reactions to create the compounds. NMR spectroscopy, including 1H, 19F, and 13C NMR, was used to confirm the structures of the synthesised compounds. The optically active derivatives' enantiomeric purity was determined using chiral HPLC. The antiviral activity of the synthesised compounds was evaluated, and it was discovered that replacing the purine fragment with a pyrimidine fragment resulted in lower anti-herpesvirus activity when compared to the lead compound, the purine conjugate. Furthermore, none of the compounds tested showed significant activity against the influenza A (H1N1) virus (Krasnov *et al.*, 2022).

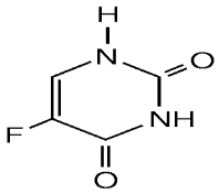
C. Anticancer Activity

Due to the existence of numerous pyrimidine-based antimetabolites, the pyrimidine moiety, when subjected to certain substitutions, exhibits compelling potential for anti-tumor activity. Structural alterations can manifest on either the pyrimidine ring itself or the associated sugar groups. Notably, the initial metabolite that emerged was 5-fluorouracil, a derivative of pyrimidine, which demonstrated remarkable anti-neoplastic properties. Subsequently, 5-thiouracil was discovered, showcasing similar anti-tumor characteristics. This emphasizes the significance of exploring and modifying the pyrimidine scaffold and its attached components, paving the way for the development of novel therapeutic agents with enhanced anti-tumor effects (Nargund *et al.*, 1992).

In a sequence of chemical processes, Awad *et al.* (2015) converged 6-amino-2-thiouracil with sulfonamides, methylated the resultant compounds, and then reacted them with bromine to form 5-bromo derivatives. By cyclocondensing the compounds with different reagents, derivatives of acetic acid, triazolopyrimidines, and thiazolopyrimidines were also produced. When the compounds' antiproliferative activity was evaluated, the human liver HEPG2 and colon cancer HT-29 cell lines showed the highest sensitivity to them. In human colon HT-29 and breast MCF-7 cell lines, the compounds showed antiproliferative action with moderate to significant growth suppression. The compounds 3a, 3b, 4a, and 10a were the most active (Awad *et al.*, 2015).



5- Thiouracil



5-Flurouracil

The synthesis of the corresponding enamines was accomplished by subjecting 5-benzoyl-, 5-carbaldehyde-/5-(3-phenyl acryloyl)-o-6-hydroxy-1H-pyrimidine-diones to amines.

The synthesized molecule was tested against 59 human tumor cell lines to determine its potential anticancer activity. This included cell lines representing various cancers, including leukemia, melanoma, colon cancer, brain cancer, lung cancer, ovarian cancer, breast cancer, and kidney cancer. This broad spectrum of tumor cell lines allowed for comprehensive investigation into the molecule's effectiveness across different types of cancer.

In another assessment of anticancer activity, Tylinska *et al*. (2021) research focuses on the design, synthesis, and evaluation of new pyrimidine derivatives for anticancer properties. The compounds investigated in this study are pyrimidine-hydrazone moieties, dihydronaphthalene, and alkylamine chains hybrids. *In vitro*, the compounds were tested for antitumor activity against colon adenocarcinoma, resistant colon adenocarcinoma, lung cancer, breast cancer, human leukemic lymphoblasts, cervical cancer, and human monocytic cells. The cytotoxicity of the compound on normal human dermal fibroblasts (NHDF) was also studied. The findings revealed that all of the compounds tested had inhibitory activity against cancer cell proliferation. Interestingly, they had a greater influence on P-glycoprotein activity in cell cultures known for being resistant to doxorubicin than doxorubicin itself. The compounds were discovered to be more lipophilic, which increases their affinity for the molecular target and facilitates transport across biological membranes. The synthetic compounds' inhibitory potential against topoisomerase II and DNA intercalating properties were also investigated using molecular docking techniques (Tylińska *et al*., 2021).

D. Anti-Fungal Activity

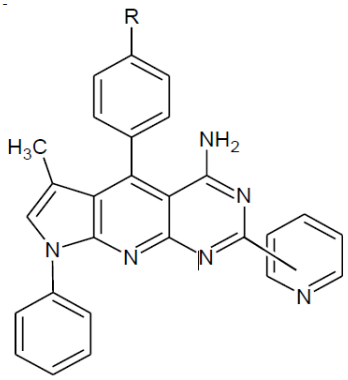
Due to their intriguing bioactivities as possible anti-fungal agents [18], fused pyrimidine derivatives, and more specifically pyrido[2,3-d]pyrimidine compounds, have received a great deal of attention. In a solvent-free microwave-assisted reaction, Acosta *et al*. (2016) synthesized a pyrazolo [4,3:5,6] pyrido [2,3-d] pyrimidine compound (Fig. 4). This novel synthetic strategy, which involved the addition of tBuOK as a catalyst to a mixture of heterocyclic o-amino nitriles and cyano pyridines, had the benefits of easy setup, mild reaction conditions, and high yields.

Clinically significant fungal species, including Candida albicans and Cryptococcus neoformans, were used to test the synthesized compounds for anti-fungal activity. Clinical isolates from patients with fungal infections as

well as a wide range of fungal strains from culture collections were used to test the most effective compounds. The purpose of this extensive evaluation was to ascertain the compounds' efficacy against the most common clinically relevant fungal species.

This study contributes to our knowledge of anti-fungal agents by exploring the pyrido [2,3-d]pyrimidine derivatives' potential as such and evaluating their efficacy against various fungal strains. The study's results help advance research and new approaches to combating fungal diseases (Acosta *et al.,* 2016).

Wu et al. looked into the antifungal properties of 17 recently created amide-modified pyrimidine derivatives. *Phomopsis* sp., *B. cinereal*, and *B. dothidea* were the *in vitro* targets for the compound tests. 5-bromo-2-fluoro-N-(2-((2-methyl-6-(trifluoromethyl)pyrimidin-4yl)oxy)phenyl)benzamide (5f) was one of the substances that was tested. Outperforming the gold standard antifungal drug Pyrimethanil, 5-bromo-2-fluoro-N-(3-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)oxy)phenyl)benzamide (5o) inhibited Phomopsis sp. 100%. With an EC50 value of 10.5 g/ml as opposed to Pyrimethanil's value of 32.1 g/ml, Compound 5o showed higher antifungal effectiveness. These pyrimidine derivatives functionalized with amides exhibited strong antifungal properties, especially against Phomopsis sp., suggesting that they could be useful antifungal drugs. This work advances our knowledge of these pyrimidine derivatives' antifungal effects and offers guidance for the development of new antifungal medications (Wu *et al.,* 2021).



Structure of pyrazolo[4,3:5,6] pyrido[2,3-d]pyrimidines

E. Anti-Inflammatory Activity

The pyrimidine nucleus has shown versatile pharmacological efficacy, leading to extensive research on its anti-inflammatory activity. As Rashid *et al.* (2021) have highlighted, anti-inflammatory effects of pyrimidines are caused by their ability to stop the expression and activity of important inflammatory mediators like inducible nitric oxide synthase, prostaglandin E2, nuclear factor B, tumor necrosis factor-, leukotrienes, and some interleukins. Evidence from the scientific literature shows that many pyrimidines have potent anti-inflammatory effects (Mery *et al.,* 1989).

Two worldwide PCT applications for 2-thiopyrimidine derivatives with strong immunomodulatory and anti-inflammatory effects have been submitted recently. In order to evaluate the anti-inflammatory properties of pyrimidine compounds, Padama Shale et al. employed the carrageen-induced rat paw edoema technique (Rashid *et al.,* 2021).

The compounds were given to albino rats ranging in weight from 150 to 200 g at a dose of 80 mg/kg. To induce edema, a carrageenan solution was injected into the left hind paw. The researchers then evaluated the effects of the pyrimidine compounds on the resulting edema. This methodology provides a standardized approach to measure the anti-inflammatory potential of the compounds in a controlled experimental setting.

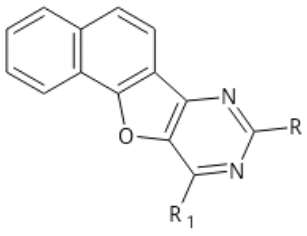
Similarly, Ahmed *et al.* (2020) conducted research aimed at developing new anti-inflammatory agents. They synthesized a 2-thioxo-1,2,3,4-tetrahydropyrimidine derivative (compound 1) through direct Biginelli condensation and used it as a starting material to synthesize a novel series of pyrimidin-2-thione derivatives (compounds 2a-d to 7a-b) (Ahmed *et al.,* 2020).

The anti-inflammatory activity of these compounds was evaluated using the carrageenan-induced rat paw edema assay, with ibuprofen as the reference drug. Molecular docking studies were also performed using SYBLYL-X v.2.1 software to investigate the binding interactions.

The obtained data demonstrated that the synthesised compounds, with ibuprofen demonstrating 69% activity, exhibited considerable anti-inflammatory action, ranging from 61% to 86%. Strong anti-inflammatory effect similar to ibuprofen was shown by compounds 2a, 2b, 2c, 2d, 3a, 3b, 3c, 3d, 7a, and 7b, especially 4 hours after carrageenan administration. With 86% activity, compound 3c showed the greatest edoema inhibition in rats. In addition, compounds 1, 2c, and 3c were examined using an in vitro enzyme assay against COX-1 and COX-2. Every substance that was examined outperformed COX-1 against COX-2.

The study provides insights into the structure-activity relationship (SAR) of the synthesized compounds and their potential as anti-inflammatory agents (Ahmed *et al.,* 2020).

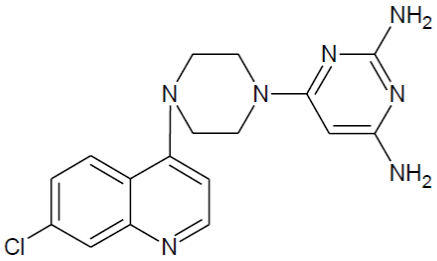
There is a growing body of knowledge about the anti-inflammatory properties of pyrimidine derivatives, and the research conducted by Padama Shale et al. and Ahmad et al. contributes to that knowledge. By using an established model for evaluating edema, the research provides valuable insights into the compounds' ability to attenuate inflammation, thus paving the way for further exploration of their therapeutic potential in inflammatory conditions (Rashid *et al.,* 2021).



R= CH_3, C_6H_5; R_1= OCH_3, OC_2H_5, NHC_2H_5, NHC_6H_5

F. Antimalarial Activity

With the fast growth of Plasmodium falciparum parasites that are resistant to several drugs, treating malaria has become an increasingly challenging therapeutic issue. The most serious occurrences in humans, including fatalities, are caused by Plasmodium falciparum infection. Formulations containing pyrimethamine and chloroquine or sulfadoxine were the first-line treatments for the management and prevention of malaria (Pretorius *et al.*, 2013).



Structure of quinoline-pyrimidine hybrid

Pretorius *et al*. (2013) synthesized a series of quinoline-pyrimidine hybrids and tested their *in vitro* anti-malarial activity and cytotoxicity. The hybrids were created using a two-step nucleophilic substitution process involving pyrimidine and quinoline moieties.

Research on the synthesis and assessment of the synthesised 2-aminopyrimidine derivatives' antitrypanosomal and antiplasmodial effects was done by Hoffelner *et al*. (2020). The compounds were synthesised by ring closure, aromatization, S-methylation, oxidation to methylsulfonyl compounds, and guanidine production with the right amines. There were phenyl and amino ring alterations in every compound. Microplate assays were used to test the synthesized 2-aminopyrimidines against Trypanosoma brucei rhodesiense, which causes sleeping sickness, and Plasmodium falciparum NF54, which causes malaria. L-6 cells—rat skeletal myoblasts—were used to test the compounds' cytotoxicity (Hoffelner *et al.*, 2020).

Some synthesized compounds showed strong antitrypanosomal and antiplasmodial activity. These novel 2-aminopyrimidine derivatives may be promising antiparasitic agents due to their structural modifications (Hoffelner *et al.*, 2020).

Iman *et al*. (2020) focused their work on the malaria-causing Plasmodium falciparum in an effort to find novel chemicals with antimalarial qualities. A number of 2-pyridyl pyrimidine derivatives were investigated for their ability to inhibit P. falciparum methionine aminopeptidase 1b (MA1b). Physicochemical characteristics and drug-receptor interactions were optimized for these analogues using QSAR analysis, molecular docking, and molecular dynamics simulations. It was determined that Tyr 260, His 277, Fe 370, Asp 240, and Trp 320 were significant residues in MA1b that influenced ligand-enzyme interactions. To learn more about compound 7, molecular dynamics simulations were performed. These findings offer crucial hints for the future development of pyrimidine-based antimalarial medications that will be more successful in treating P. falciparum malaria (Iman *et al.*, 2020).

G. Anti-Depressants and Anti-Convulsants Activity

Antidepressants and anticonvulsants are two often prescribed drugs that target the central nervous system (CNS). A group of 5-alkoxytetrazolo[1,5-c]thieno[2,3-e]pyrimidine derivatives were investigated for possible anticonvulsant and antidepressant effects in a recent study.

One compound within this series, specifically 5-(2,4-dichlorobenzyloxy)tetrazolo[1,5-c]thieno[2,3-e]pyrimidine, demonstrated significant activity at a dosage of 100 mg/kg. It exhibited a substantial reduction in the immobility period, indicative of potential antidepressant effects. This compound reduced the immobility period by approximately 51.62 percent, suggesting its potential in alleviating depressive symptoms.

Assessing the anticonvulsant and antidepressant properties of these 5-alkoxytetrazolo[1,5-c]thieno[2,3-e]pyrimidine derivatives offers important information about their potential pharmacological use in the management of central nervous system disorders. Further research in this area may lead to the discovery of novel treatments for mental health conditions like depression and epilepsy (Wang *et al.*, 2012).

In order to find possible novel triazolopyrimidines derivatives for usage as antiepileptic medications (AEDs), Song *et al*. (2022) undertook a study. They created the triazolopyrimidines (3a-3i and 6a-6e) and pyrazolopyrimidines (4a-4i), and they investigated the anticonvulsant properties of these compounds in living animals. The findings showed that in maximum electroshock (MES) and pentetrazol (PTZ)-induced seizure models, triazolopyrimidines exhibited strong anticonvulsive activity, whereas pyrazolopyrimidines showed negligible or no protective effects (Song, *et al.*, 2022).

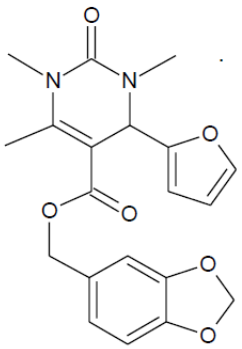
Compound 6d was the most effective derivative, with an ED50 against MES-induced seizures of 15.8 and 14.1 mg/kg, respectively, and against PTZ-induced seizures of 14.1 mg/kg. Compound 6d's protection index (PI) was also greater than that of AEDs that are currently on the market, such as valproate, carbamazepine, and diazepam. Several seizure models demonstrated the antiepileptic effects. The anticonvulsant action of compound 6d is attributed to benzodiazepine (BZD) receptors, a subtype of GABA receptor, according to additional studies (Song *et al.*, 2022).

H. Antithyroid Activity

The production and assessment of iodide translocation, the first and rate-limiting stage in the biosynthesis of the iodinated hormones T3 (triiodothyronine) and T4 (thyroxine), were the main topics of Lacotte *et al.* (2013) investigation. The sodium iodide symporter (NIS), a glycoprotein with 13 putative transmembrane domains, is essential to this function. NIS is predominantly located in the thyroid gland, but it is also found in the salivary glands, the mucosa of the stomach, and the mammary glands during lactation.

The researchers aimed to understand and characterize the mechanism of iodide translocation mediated by NIS. By synthesizing and evaluating the process, they

sought to shed light on the functional aspects of this crucial step in hormone biosynthesis. This research contributes to our knowledge of thyroid function and the regulation of iodine transport in various tissues, highlighting the significance of NIS in the context of thyroid hormone production and its potential involvement in lactation-related processes.



Structure of dihydropyrimidin-2-ones

Dihydropyrimidin-2-ones (DHPMs) were tested for their capacity to prevent iodide uptake in rat thyroid cells. Using the multi-component Biginelli reaction, the synthesis was completed. In a test using cells, the capacity of 12 substances to inhibit the sodium iodide symporter (NIS) was investigated. One recently created derivative had an IC50 value of only 65 pM, indicating remarkably powerful behaviour. This work contributes to the development of antithyroid medications (Lacotte *et al.*, 2013).

I. Anti-Alzheimer Activity

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive loss of memory and cognitive function. Its characteristic features include extracellular amyloid-(A) plaques, the formation of intracellular neurofibrillary tangles from hyperphosphorylated tau protein, and the death of neurons in the brain. A characteristic that is frequently seen in people with late-onset Alzheimer's disease is a dysfunction in respiratory complex IV, which is related to cellular respiration.

It is interesting to note that there is a connection, specifically upstream of respiratory complex IV, between the mitochondrial respiratory chain and the de novo pyrimidine production pathway. The metabolic process known as "de novo pyrimidine biosynthesis pathway" is in charge of producing pyrimidine nucleotides, which are necessary building blocks of DNA and RNA. It has been discovered that this pathway is linked to the mitochondrial respiratory chain, which is essential for the cellular synthesis of energy.

The link between the de novo pyrimidine biosynthesis pathway and the mitochondrial respiratory chain suggests a potential involvement of pyrimidine metabolism in the pathogenesis of Alzheimer's disease. Further research in this area may help elucidate the underlying mechanisms and potentially uncover new therapeutic targets for the treatment of this neurodegenerative disorder. Insights into the pathophysiology of AD and new therapeutic approaches can both be gained from an understanding of the interactions between these pathways (Pesini *et al.*, 2019).

J. Anti-Angiogenic Activity

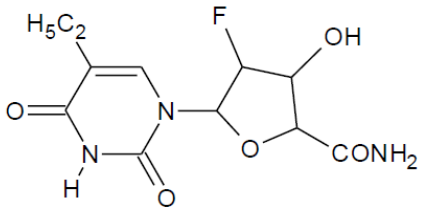
Organ development depends on angiogenesis, a physiological process that creates new blood vessels from the vasculature that already exists. On the other hand, disruption of the regulatory mechanisms governing angiogenesis can play a role in the development and advancement of a number of illnesses, including as rheumatoid arthritis, psoriasis, ocular neovascularization, inflammation, tumour growth, and metastasis.

Vascular endothelial growth factors (VEGFs) are an important class of factors in angiogenesis. Placental Growth Factor (PlGF), VEGF-A (often referred to as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and VEGF-F are members of the VEGF family. These growth factors play a role in angiogenesis stimulation and the development of new blood vessels.

The goal of Perspicace *et al.* (2013) research is to cure illnesses associated to angiogenesis by developing thieno pyrimidines as VEGFR-2 inhibitors, a receptor implicated in VEGF signalling. Although angiogenesis is essential for the growth of organs, it can also be a factor in many other illnesses. The family of VEGFs, which includes VEGF-A, is crucial for angiogenesis. After creating several compounds, the scientists found a lead molecule that, at low doses, inhibited both VEGFR-2 and human umbilical vein endothelial cells (HUVECs). The substance successfully prevented the development of VEGF-induced endothelial cell tubes, according to *in vitro* tests. In terms of efficacy, the molecule fared better than Sunitinib, the gold standard medication. These results imply that the found molecule may serve as a model for the creation of new anti-angiogenic drugs for the treatment of illnesses associated with angiogenesis (Perspicace *et al.*, 2013).

K. Anti-Hepatitis Activity

Hepatitis B virus (HBV) and the hepatitis C virus (HCV) infections, which are common causes of chronic liver disease, can coexist in a given individual. Liver cancer, cirrhosis, and hepatocellular carcinoma are all potentially fatal conditions that have been linked to the co-infection of HBV and HCV (Shakya *et al.*, 2014).



Structure of 4′-carboxamide pyrimidine nucleoside

According to Shakya *et al.* (2014) a novel family of pyrimidine nucleosides containing 4-carboxymethyl and 4-carboxamide functional groups has been synthesised and shown potential against the hepatitis C virus. The anti-HCV activity and toxicity of any of the drugs tested positive. The results showed that these substances' anti-HCV properties were on par with those of ribavirin (EC50 = 81.9 M). When paired with

ribavirin, the most potent counterpart of the fully synthesised chemicals suppresses HCV RNA replication (Shakya *et al.*, 2014).

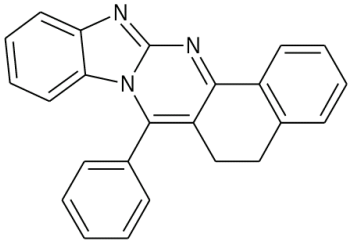
In order to find new non-nucleoside inhibitors for the treatment of hepatitis B virus (HBV), Wang *et al.* (2018) conducted a study on 2-arylthio-5-iodo pyrimidine derivatives. The researchers wanted to evaluate these compounds' anti-HBV activity and investigate their mechanism of action. They isolated the HBV polymerase and created a novel non-radioisotopic assay to measure its activity. The study's findings revealed that 2-arylthio-5-iodo pyrimidine derivatives had promising activity against HBV polymerase, indicating their potential as anti-HBV agents. In addition, the researchers created pharmacophore models to aid in future optimization of these lead compounds. This study lays the groundwork for the future development of effective non-nucleoside anti-HBV agents (Wang *et al.*, 2018).

L. Anti-diabetic Activity

Diabetes is the most common metabolic disorder in both developing and developed countries, as well as a well-known global health issue. The WHO predicts that the number of cases will rise from 171 million in 2000 to 366 million by 2030. Some pyrimidine derivatives may prove useful in the fight against diabetes due to their unique properties. Heterocyclic compounds with pyrimidine derivatives have significant chemical and pharmacological importance because of the multiple roles they play in biology (Bassyouni *et al.*, 2021).

Bassyouni *et al*. (2021) focus on the preparation of pyrimidine derivatives as potential antidiabetic and antimicrobial agents in their study, which addresses the significant global health issue of diabetes. With diabetes becoming more common around the world, the development of new treatment options is critical. The researchers compared thiazolopyrimidine derivatives to the reference drug glimepiride *in vivo* effects on serum glucose concentration, cholesterol levels, and antioxidant activity in rats. Compound 5 demonstrated promising results, particularly in terms of liver health maintenance. The compounds' antimicrobial activities were also tested against various bacterial strains and fungi, with compounds 4 and 5 showing significant inhibition. Computational analysis and molecular modelling were used to generate protein targets for these drugs, and the docking studies agreed with the *in vitro* and *in vivo* results. This extensive study sheds light on the potential of these pyrimidine derivatives as anti-diabetic and antimicrobial agents (Bassyouni *et al.*, 2021).

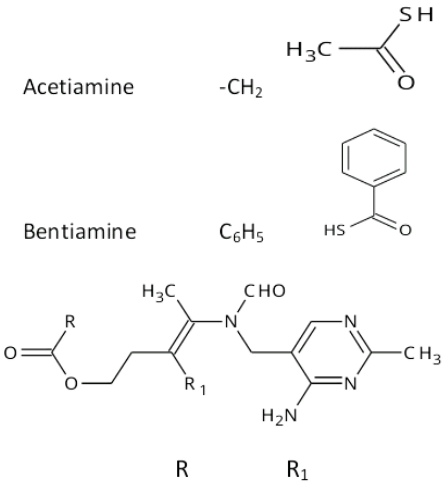
Russell *et al*. (1988) created new pyrimidine derivatives that contained thiazolidinedione. The goal was to assess the glucose and lipid lowering activity of these compounds, using pioglitazone and rosiglitazone as controls. Furthermore, the hypoglycemic activity of the synthesised azolopyrimidine derivatives and compounds was evaluated. with an objective to explore their potential as glucose and lipid management agents. The study provides insights into the effectiveness of these pyrimidine derivatives by comparing them to established reference compounds (Russell *et al.*, 1988).



Azolopyrimidine

M. Analgesic Activity

In their work, Ganzevoort *et al.* (2004) looked into novel lipidsoluble thiamine compounds such acetiamine and Benti-amine. Numerous ailments, including beriberi, polyneuritis, encephalopathy, pain, malnourishment, drunkenness, and long-term insulin-dependent diabetic mellitus, may be treated by these substances. The scientists evaluated the potency of these substances using the acid-induced writhing test, a widely used technique to gauge analgesic action. They contrasted the results with diclofenac sodium, a common painkiller. This study clarifies the possible medicinal uses of lipid soluble thiamine compounds, especially in the treatment of diabetes and the control of pain (Ganzevoort *et al.*, 2004).



CONCLUSIONS

The work offers fresh insights into the applications of pyrimidine derivatives in medicine and pharmacology. This overview demonstrates the wide range of illnesses for which pyrimidine derivatives have been investigated. Pyrimidines and their derivatives have been linked to a variety of pharmacological effects, such as those that are antimicrobial, antiviral, anticancer, antifungal, anti-inflammatory, antimalarial, antidepressant, anticonvulsant, antithyroid, anti-alzheimer, anti-angiogenic, anti-hepatitis, anti-diabetic, and analgesic.

FUTURE SCOPE

It is an important substance for the pharmaceutical sector. More investigation into this area is still necessary in the hopes of finding a unique pharmacological activity. In addition, greater research on pyrimidine derivatives is desperately required because of medication resistance to already prescribed

treatments. A vast literature has accumulated over the years, and pyrimidine chemistry is still a thriving field. In comparison to older compounds, the biological profiles of this new generation of pyrimidines represent significant progress.

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Conflict of Interest. None.

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