*Biological Forum – An International Journal* **15(4): 963-976(2023)**

**ISSN No. (Print): 0975-1130**
**ISSN No. (Online): 2249-3239**

# Exploring the Potential of Pyrimidine: A Comprehensive Review of its Biological Roles, Medicinal Applications, and Synthetic Methodologies in Drug Development

***Ajay A. Kumbhar, Harichandra A. Parbat and Anna Pratima Nikalje****
*Department of Chemistry, Jhon Wilson Education society's,*
*Wilson College (Autonomous), Mumbai (Maharashtra), India.*

*(Corresponding author: Anna Pratima Nikalje*)*
*(Received: 17 February 2023; Revised: 15 March 2023; Accepted: 19 March 2023; Published: 20 April 2023)*
*(Published by Research Trend)*

**ABSTRACT: Medical chemistry focuses on developing and producing medicinal compounds or pharmaceutical agents that have positive effects on human health and well-being. About half of modern organic chemistry research focuses on heterocyclic chemicals, which have been shown to be both widely and economically useful as therapeutic agents. Pyrimidines, a notable heterocyclic compound, are among the most notable due to their notable pharmacological effects. They are vital constituents of cellular structures and all forms of organic life, and their biological activities are essential for the development and release of effective new drugs.**

**Pyrimidine and its derivatives exhibit a wide range of biological and pharmacological actions, including but not limited to anticonvulsant, antibacterial, antifungal, antiviral, and anticancer characteristics. The ability of pyrimidine to exhibit synthetic flexibility has enabled the production of several derivatives with varying structures. This has greatly eased the investigation of a broad spectrum of biological targets. This research provides a comprehensive description of the biological roles associated with the pyrimidine scaffold. Due to the significant biological activities exhibited by pyrimidine, the field of medicinal chemistry maintains a continued interest in the pyrimidine skeleton as a valuable component for drug development. Consequently, the development of practical and dependable methodologies for the synthesis of pyrimidine molecules is of utmost importance. This article provides an overview of the anticancer and antibacterial capabilities associated with the pyrimidine scaffold. The scientific discoveries presented in this publication possess the potential to serve as a source of inspiration for future scholars, encouraging them to explore the intricacies of this particular heterocyclic scaffold. This review paper has the potential to draw the attention of researchers who are interested in the structural design and development of innovative active pyrimidine scaffolds, aiming to enhance their activity while minimising their toxicity.**

**Keywords:** Pyrimidine, Drug Development, Synthesis, Biological Activities.

## INTRODUCTION

A chemist practising in the discipline of medical chemistry works towards the goal of creating a pharmaceutical agent or medicinal chemical that improves people's health. The primary goal of medicinal chemistry research is to discover and develop effective new drugs for the treatment of a wide range of medical conditions. Heterocyclic compounds are the subject of approximately 50% of current organic chemistry study. Heterocyclic compounds provide an incredible array of structural possibilities and have been proven to be both universally and economically beneficial as medicinal agents. Heterocyclic ring structures are found in a wide variety of substances, including alkaloids, essential amino acids, vitamins, haemoglobin, hormones, a vast number of synthetic drugs, and even some colours. Many heterocyclic compounds that are synthesised, like pyrrole, pyrrolidine, furan, thiophene, piperazine, pyridine, and thiazole, have important applications and are used as intermediates in various synthesis routes (Mitra & Ghosh 2021; Moradivalikboni *et al*., 2015a,b; Tiwari & Singh 2009).

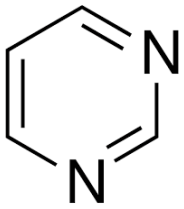


**Fig. 1.** Basic structure of pyrimidine.

Among the heterocyclic chemicals, pyrimidines stand out as having important pharmacological roles (Miller *et al*., 2019). Pinner coined the term pyrimidine by combining the names pyridine and amidine. There is a large class of heterocyclic compounds that consists of pyrimidines(1,3-diazines) and their fused analogues. Because of their important pharmacological effects, pyrimidines are among the most well-known heterocyclic chemicals. These compounds are fundamental to the construction of all living cells. The pyrimidine found in DNA and RNA has been linked to a number of therapeutic benefits (Meneghesso *et al*., 2012).

Medicinal chemists have long found pyrimidine to be a particularly intriguing heterocyclic moiety, and

extensive study of pyrimidines has resulted in the development and release of a number of effective new drugs. Pyrimidine derivatives are crucial pharmaceuticals due to their biological actions. After hydrolyzing nucleic acids, scientists have isolated many different types of pyrimidines. To fully grasp the biochemical application of pyrimidines and the pharmacological metabolism of pyrimidine derivatives, it is crucial to have a firm grasp on their unusual metabolism. The commencement of fused pyrimidine chemistry can be traced back to the year 1776, when uric acid was discovered by Scheele. There are three isomeric diazines, one of which is pyrimidine. Natural substances like nucleic acids rely on the presence of basic fused pyrimidines like purines and pteridines because of their inherent biological activity. Prazosin, quinethazone, methotrexate, folic acid, and riboflavin are all pyrimidine derivatives with biological activity. Many pyrimidine scaffolds were developed and utilised by medicinal chemists to design novel therapeutics with a broad range of pharmacological activities including antimicrobial (Marinescu, 2021), antibacterial (Shahi *et al*., 2016), antifungal (Chen *et al*., 2008), herbicidal activity (Ma *et al*., 2016), anti-inflammatory (Nettekoven *et al*, 2016), therapeutic potentiality (Gajera *et al*., 2016), antitubercular (Zuniga *et al*., 2017), anticancer (Wisniewska *et al*., 2019), anticonvulsant (Guan *et al*., 2012), antileishmanial (Ramirez-Macias *et al*., 2012), antihypertensive (Ali *et al*., 2011; Zhang *et al*., 2010), cytotoxicity (Lakomska *et al*., 2019), and antitumor (Fandzloch & Lakomska 2018) effects. Recent medicinal applications and structure activity relationship of pyrimidine associated analogues from 2017 to 2021 are discussed in this review manuscript.

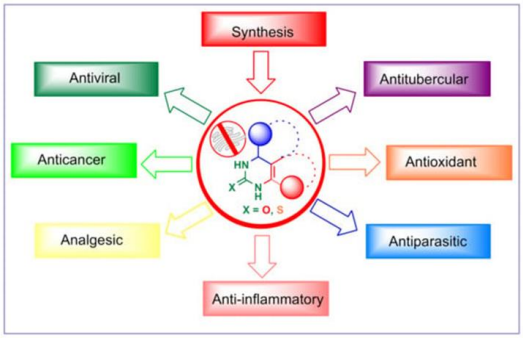


**Fig. 2.** Illustration showing the steps involved in the production and medicinal uses of antibacterial Biginelli-mediated pyrimidine compounds (Marinescu, 2021).

## CHEMISTRY

Pyrimidine is a member of the nitrogen-rich heterocycle family. The nitrogen atoms in pyrimidine are located in the first and third positions of its six-membered heterocyclic organic ring structure. Pyrimidines have been isolated from nucleic acid via hydrolysis. The pyrimidines are relatively insoluble in water because they are hydrophobic, even at the physiologically neutral pH of the cell. Purines and pyrimidines are more soluble in water and more amenable to ionisation at acidic or alkaline pH (Meneghesso *et al*., 2012).

Analogues derived from aryl ring substitution, derivatization of pyrimidine nitrogen, and carbon substitutions at the 2, 4, 5, and 6 positions are all possible thanks to pyrimidine's synthetic versatility (Selvam *et al*., 2015). Because pyrimidines are structurally similar to pyridine, the difficulty of electrophilic aromatic substitution and the ease of nucleophilic aromatic substitution both rise with the amount of nitrogen atoms in the ring. One example of the latter category of reactions is the exchange of the amino group in 2-aminopyrimidine for a chlorine atom, or vice versa. If the resonance stabilisation of pyrimidines is diminished, then reactions involving addition and ring cleavage are more likely to occur than replacements. For instance, consider the Dimroth rearrangement. Since pyrimidines are less basic than pyridine, they present greater challenges for N-alkylation and N-oxidation. The pKa value of protonated pyrimidine is lower than that of pyridine (5.23) due to its protonation. Pyrimidines can also be made in a laboratory using organic synthesis. Most pyrimidines are synthesised via the condensation reaction of a 3-carbon molecule with an amidine structure substance, where R can be OH (urea), SH (sulfamethoxamine), or SR (thiourea or its S-derivative). This reaction takes place in the presence of a catalyst such as sodium hydroxide or sodium ethoxide. The production of 4-hydroxy-2,6-dimethylpyrimidine via the condensation reaction of acetamidine and ethyl acetoacetate is a prototypical example of the aforementioned phenomena. The traditional Biginelli reaction is one such technique. 3,4-dihydropyrimidin-2(1H)-ones are synthesised from an aryl aldehyde (such as benzaldehyde), ethyl acetoacetate, and urea via a multi-component chemical reaction known as the Biginelli reaction (Meneghesso *et al*., 2012; Marinescu, 2021).

Therapeutic uses of pyrimidine derivatives have long been recognised in the field of medicinal chemistry. Understanding the biochemical utilisation and pharmacological metabolism of pyrimidines is greatly enhanced by studying their distinctive metabolic processes. One possible explanation for the efficacy of nucleic acids, DNA, and RNA is that they contain a pyrimidine base, like thymine, cytosine, and uracil (Shahi *et al*., 2016). Most clinically useful heterocyclic drugs contain a hydrogen donor/acceptor unit, a carbonyl group, and either one or two phenyl rings attached to nitrogen hetero atoms. Important core fragments were identified in all of the initial investigations by the hydrogen donor/acceptor unit (HAD), the hydrophobic domain (A; aryl ring substituted/unsubstituted), and the electron donor atom (D; see also (Selvam *et al*., 2015)). These properties were shared by the structures of numerous commonly used medications, including uramustine, piritrexim isothiocyanate, tegafur, floxuridine, fluorouracil, cytarabine, methotrexate, and others (Selvam *et al*., 2015).

## BIOLOGICAL SIGNIFICANCE

Antimicrobial resistance puts the prevention of infectious diseases and the treatment of those diseases caused by fungi, bacteria, viruses, and parasites in jeopardy. Infectious diseases are becoming an increasingly significant risk to the general health of people all over the world. Every society on the planet is required to take immediate and preventative action (Cassir *et al*., 2014). As a result of repeated exposure to antimicrobial agents like fungicides, antivirals, and antibiotics, microorganisms like viruses, bacteria, parasites, and fungi can become resistant to these treatments. Over time, bacteria and other microbes develop and spread resistance to antimicrobial drugs. Therefore, most drugs will become practically ineffective in treatment, and diseases and infections will persist in the human body, heightening the risk of proliferation in communities and endangering our capacity to treat infectious and common diseases that are known to cause death (Goossens *et al*., 2005). Natural and spontaneous evolution of antimicrobial resistance typically results from genetic changes. Antimicrobial resistance is the result of natural selection acting on random mutations. When a bacterium creates a new gene, it can transfer that gene's genetic code horizontally. Multiple resistant genes can be found in multi-resistance bacteria. Bacteria are put under stress because of antimicrobial resistance, but some strains can overcome this by changing their DNA. The next generation inherits this characteristic and is thus characterised by a total lack of susceptibility to antimicrobial treatment. There has been an increase in the prevalence of antimicrobial resistance due to inadequate infection control, a lack of adequate hygienic conditions, and insufficient proper handling of all types of food. Because they require more treatment for their infections, patients with drug-resistant bacteria have a higher risk of poor clinical outcomes and acute death than those with infections caused by non-resistant strains of the same microbes and bacteria (Mishra *et al*., 2012). Resistance to sulfonamide drugs and TMP in various bacterial strains has prompted us to develop new compounds containing the sulfonamide group as DHPS inhibitors bonded to the six-membered ring, such as pyridine substituted with the amino/hydroxyl group. Pyrimidine is the parent substance that is used in the synthesis of a wide variety of heterocyclic compounds as well as the raw material that is used in the synthesis of new molecules (Avupati & Yejella 2014). Natural products, agrochemicals, and veterinary products were found to contain pyrimidine ring complexes with a variety of heterocyclic moieties, which were found to be essential components. For the treatment of bacterial and fungal infections, there is a wide variety of antimicrobial medication available, including ciprofloxacin, griseofulvin, chloramphenicol, and nystatin (Gupta *et al*., 2013).

Similarly, Cancer is a complex disease that contributes significantly to mortality rates in industrialised nations. Cancer causes one in every eight deaths worldwide and is the leading killer in the United States, second only to coronary heart disease. While chemotherapy is the gold standard for treating cancer, the use of current chemotherapeutics is often constrained by their unpleasant side effects. Finding novel molecules and therapeutic targets is crucial in the fight against cancer (Nagender *et al*., 2014).

## CONTEMPORARY RESEARCH

Tarceva® (Erlotinib) is a widely used pyrimidine-based anticancer medication. For the treatment of pancreatic cancer and non-small cell lung cancer (NSCLC), the Food and Drug Administration has authorised the use of this medication. In addition, triazolo pyrimidines, also known as Trapidil, have been shown to be effective in the prevention of parathyroid bone disease (Lotinun *et al*., 2003) and in the treatment of memory disorders (Van Roosbroeck *et al*., 2018) by acting as a platelet-derived growth factor antagonist and a phosphodiesterase inhibitor, respectively.

The term "antimicrobials" refers to a class of pharmaceuticals that includes both folic acid antagonists (antifolates) and sulfa drugs (pyrimidine sulfonamides). Brodiprim (Sader *et al*., 2009), a folic acid antagonist that has shown efficacy as an antibacterial treatment, and Iclaprim, a new dihydrofolate inhibitor with selective characteristics, are only two examples of the many drugs in this class. Notably, Iclaprim exhibits activity against methicillin-resistant strains. Trimethoprim is a pharmacological agent with antibacterial properties that exerts its effects by selectively inhibiting the enzyme dihydrofolate reductase (DHFR) in bacteria. Pyrimethamine is a pharmacological agent that exhibits selectivity in inhibiting the dihydrofolate reductase (DHFR) enzyme specifically in plasmodia responsible for causing malaria (Hawser *et al*., 2006).

Several pyrazolopyrimidines are effective against bacteria and fungi (Khobragade *et al*., 2010). Numerous antibiotics incorporate a pyrimidine component within their chemical structure, exemplified as Amicetine, Bacimethrin, and Bleomycin. Recently, several new synthetic methods for preparing pyrazolopyrimidine derivatives were reported, which have shown promise as potential new classes of anticancer and antimicrobial agents (Elgemeie *et al*., 2017; Elgemeie *et al*., 2016).

A novel line of pyrido thienopyrimidine derivatives was designed and evaluated for its efficacy against bacteria and tumours (El-Deen *et al*., 2022). These compounds were synthesised by reacting the 3-amino thieno[2,3-b] pyridine-2-carboxamide 1 with aromatic aldehydes to form the pivotal intermediates 2a and 2b. These intermediates were then further treated to obtain the final 2,4-disubstituted-pyrido[3,2-d:4,5-d']thieno[2,3-d]pyrimidines, designated as 3a, 3b, 11a, and 11b.

Antimicrobial screening was performed on the newly synthesised compounds against many different types of bacteria and fungi. Antimicrobial activity was most prominent in compounds 6c, 8b, 9a, and 9b, having MIC values between 4 and 16 g/mL against the investigated bacteria. In addition, the cytotoxic effects of compounds 2a, 2b, 11a, and 11b were tested in

HepG-2 and MCF-7 cancer cell lines. Notably, compounds 2b, 4a, 6a, 7b, 7c, and 9a displayed strong anticancer activity. The inhibitory effects of compounds 6a, 7b, 7c, and 9a were also investigated on the EGFRWT enzyme, showing potential mechanisms of action. The findings underscore the considerable antimicrobial and anticancer potential of specific compounds, opening avenues for further research and advancements in therapeutic interventions (El-Deen *et al*., 2022).

El-Atawy *et al*. (2022) conducted an extensive study involving the synthesis and analysis of diverse pyrimidines with distinct structures. Various analytical techniques were employed to confirm the chemical structures of the compounds. The synthesized pyrimidines were evaluated for their potential to inhibit tumor growth across several human cancer cell lines (El-Atawy *et al*., 2022).

Notably, compounds 3b and 3d displayed promising anti-proliferative activity against prostate carcinoma PC3 cells, outperforming the reference drug vinblastine sulfate. Compounds 3b, 3f, 3g, 3h, and 5 exhibited enhanced safety and selectivity compared to vinblastine sulfate. The compounds adhered to Lipinski's Rule of Five, indicating potential oral bioavailability. Additionally, compound 3b demonstrated potent anticancer activity against the PC3 cell line and greater selectivity towards cancer cells than normal cells. Molecular docking simulations suggested a potential mechanism of action involving interaction with Bcl-2.

Overall, El-Atawy *et al*. (2022) study presents a comprehensive approach to identifying effective pyrimidine-based compounds for combating human cancer cells, particularly prostate carcinoma. The compounds' safety, bioavailability, and potential mechanisms of action offer promising avenues for targeted cancer therapy (El-Atawy *et al*., 2022).

Prabhakar *et al*. (2017) introduced a five-step synthesis process for a novel series of N-(4-(substituted amino) thieno[2,3-d]pyrimidin-2-yl) thiophene/Furan-2-carboxamide (7 a-j) derivatives. This approach provided mild reaction conditions, ease of execution, and satisfactory yields. These compounds were evaluated for their antimicrobial activity against several bacterial and fungal strains, with notable activity observed for compounds 8j, 8i, 8h, and 8g (El-Atawy *et al*., 2022).

Moreover, compounds 2a, 2b, 11a, and 11b were examined for cytotoxicity against HepG-2 and MCF-7 cancer cell lines, showing potent anticancer activity. Some compounds were identified as potential leads for further investigation based on their mechanisms of action (Prabhakar *et al*., 2017).

Narwal *et al*. (2017) generated a series of pyrimidine derivatives and confirmed their structures using IR, $^{1}H/^{13}C$-NMR, and mass spectroscopy. These derivatives were then tested for antimicrobial activity against a variety of bacterial and fungal strains. The minimum inhibitory concentration (MIC) in M/ml was determined using the tube dilution method. The values for the minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were also recorded, indicating the lowest compound concentration that resulted in a significant reduction (96-98%) in bacterial and fungal growth (Narwal *et al*., 2017).

Overall, the antimicrobial activity of the synthesised derivatives was significant. Compounds 2, 5, 10, 11, and 12 were particularly effective against Gram-positive (*S. aureus* and *B. subtilis*) and Gram-negative (*E. coli*, *P. aeruginosa*, and *S. enterica*) bacterial strains, as well as fungal strains (*C. albicans* and *A. niger*). Surprisingly, the presence of electron-withdrawing groups in compounds 2, 5, 11, and 12 increased their antimicrobial potential, making them more effective than the standard drugs cefadroxil and fluconazole (Narwal *et al*., 2017).

The study shows that the synthesised pyrimidine derivatives have promising antimicrobial activity, outperforming standard drugs. The findings highlight the importance of electron-withdrawing groups in enhancing antimicrobial potential and point to these compounds as potential future research and development candidates (Narwal *et al*., 2017).

Triazolo [4, 3-a] pyrimidines, pyrido [2, 3-d] pyrimidines, and pyramido [4, 5-d] pyrimidine systems were newly synthesised (Shaaban *et al*., 2018). The novel compounds were compared to the gold standards, gentamicin, and ketoconazole, for their antibacterial and antifungal efficacy. To kill off Candida albicans, compound 14b was more effective than the standard antifungal medication ketoconazole (MIC=20 g/ml). Against *S. aureus* and *E. coli*, compound 8c's MIC=19.53 g/ml was higher than gentamicin's MIC=24 g/ml and MIC=30 g/ml. The minimum inhibitory concentration (MIC) of compound 11c against B. subtilis was 19.53 g/ml, while the MIC of gentamicin was 26 g/ml. All of the synthesised derivatives were tested for anticancer and antimicrobial activity. Among the investigated compounds, Compound 7 showed the greatest activity against a wide range of cancer cell lines (Shaaban *et al*., 2018).

Abdelgawad (2019) produced a series of novel azo-pyrimidine derivatives (Abdelgawad, 2019). The antibacterial activity of new azo compounds against Gram-positive microorganisms (*Sarcina lutea*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecalis*) and Gram-negative microorganisms (*Pseudomonas aeruginosa*) was evaluated. Compound 31, 5-[(3,5-Dichloro-phenyl)-hydrazone]-2-thioxo-dihydroyrimidine-4,6-dione, was discovered to be the most active against the bacterial strains among the synthesised derivatives. They concluded that the thiopyrimidine ring broadens the antibacterial spectrum of the new azo-compounds.

In order to find new antibacterial agents, Fang *et al*. (2019) synthesised a series of novel 2, 4-disubstituted-6-thiophenyl-pyrimidine derivatives and tested them against bacteria that cause common illnesses in humans (Fang *et al.*, 2019). Both MRSA and VRE are effectively inhibited by the compounds. Compound 33 is more effective as an antibiotic against MRSA and VREs (MIC values: 2 mg/mL) than either methicillin or

vancomycin. Compound 33 inhibited ATPase activity and Fts Z polymerization, as shown by *in vitro* and *in vivo* experiments. This chemical inhibits bacterial cell division by attaching to the GTP binding site of Fts Z, killing out the bacteria in the process. While *S. aureus* resistant to penicillin 33 was not observed in the resistance creation trials, methicillin resistance occurred.

The antiproliferative activity of a newly synthesised series of 2-phenylpyrimidine coumarin derivatives was tested *in vitro* against the CNE2, KB, and Cal27 cancer cell lines (Lv *et al*., 2017). Most of the derivatives showed promise in inhibiting tumour cell proliferation, with Compound B32 showing the most promising antiproliferative activity and being on par with the gold standard drug.

Novel derivatives of Pyrazolo [1, 5-a] pyrimidine were synthesised and screened for antibacterial and antifungal activities (Abdallah & Galal 2018). All of the compounds that were prepared were tested for antimicrobial activity, and the MICs for the most effective ones were then determined in this study. The *in vitro* activity and the molecular docking study were consistent with one another. Antimicrobial compounds with the highest docking scores (7b, 7c, 14a, 14b, 14e, and 14i) were tested for their ability to inhibit RNA polymerase. In comparison to the gold standard ampicillin, the RNA polymerase enzyme was most effectively inhibited by compound 7b.

Similarly, Jat *et al*. synthesised novel pyrimidine derivatives (compounds 5–11) in three stages. Claisen-Schmidt condensation of aromatic aldehydes with 2-acetyl pyridine/3-acetylpyridine in methanol in the presence of aqueous NaOH was used to produce chalcones containing a -$NO_2$ functional group in the first step. The -$NO_2$ group was reduced to -$NH_2$ in the second stage. In the presence of N,N-diisopropylethylamine, $NH_2$-containing compounds were reacted with various dichlorothienopyrimidines and dichlorofuropyrimidines to produce pyrimidine derivatives (Bhagchand, 2019).

*In vitro* research was conducted on the antibacterial and antifungal activity of pyrimidine derivatives. Antibacterial activity of synthesised pyrimidine derivatives against the bacteria *Escherichia coli* and *Bacillus sphaericus* has been evaluated. On *Aspergillus niger* and *Penicillium funiculosum*, the antifungal activity of a pyrimidine derivative has been evaluated. Compounds 10 and 11 demonstrated significant antibacterial activity, while compounds 5, 6, and 8 demonstrated moderate to excellent antibacterial activity. Compounds 5, 6, and 10 displayed significant antifungal activity against *P. funiculosum*, while compounds 7 and 8 displayed moderate antifungal activity against *A. niger*. Antibacterial and antifungal activity of pyrimidine derivatives at 1 g/mL. Several newly synthesised pyrimidine derivatives exhibited strong-to-moderate antibacterial and antifungal activity (Bhagchand, 2019).

Chen *et al*. utilised a convergent synthetic route to produce a series of novel 1,3,4-thiadiazole derivatives of glucosides from D-glucose and 5-amino-1,3,4-thiadiazole-2-thiol in high yields. Through acetylation, bromination, thioetherification, chlorination, and condensation, a series of novel glucoside 1,3,4-thiadiazole derivatives were prepared (Chen *et al*., 2021). Five different fungi, including *P. infestans, G. zeae, B. dothidea, Phomopsis* sp., and *T. cucumeris*, were used to evaluate the *in vitro* antifungal activity of the target compounds. The target compounds exhibited moderate to good antifungal activities against *P. infestans, G. zeae, B. dothidea, Phomopsis* sp., and *T. cucumeris*, with inhibitory rates ranging from 19.8 to 83.5%, 35.6 to 73.1%, 22.1 to 62.0%, and 21.0 to 64.0%, respectively. At 50 g/ml, the inhibitory rates of the target compounds against *G. zeaein* ranged from 35.6% to 73.1%, which was greater than the previously reported inhibitory activity of N-(2-chloro-4-phenyl-5-(trifluoromethyl) cyclopenta-1,4-dien-1-yl)-5-((4-nitrobenzoyl)thio).-1,3,4-thiadiazol- 2-amine against *G. zeae* (23.9%) at the 50 µg/ml (Chen *et al*., 2021).

Compounds 4i and 4q exhibited greater antifungal activity against *P. infestans* than Dimethomorph, with inhibition rates of 83.5% and 81.1%, respectively. On the basis of preliminary antifungal bioassays, the $EC_{50}$ values of partial compounds against *P. infestans* were evaluated. Compounds 4i exhibited bioactivities against *P. infestans* with $EC_{50}$ values of 3.43 g/ml, which were greater than those of Dimethomorph (5.52 g/ml) It was determined through structure-activity relationships (SAR) analysis uncovered obvious SAR against *P. infestans*. Examination of based on the chemical structures of the target compounds, group R in the target compounds has a significant impact on *P. infestans*-resistant antifungal activity. Utilising a fluorinated or nitrified substituent (4-F and 4-$NO_2$) on the phenyl ring, the nitrified substituent compounds demonstrated improved bioactivity against *P. infestans* (both 4i and 4q). Additionally, the location of substituent groups in the phenyl ring also contributes significantly to antifungal activity Against P. infestans, phenyl rings with four substituents (4-F or 4-$NO_2$) exhibited greater antifungal activity than other phenyl rings (Chen *et al*., 2021).

Alqahtani *et al* conducted a synthesis of novel tri-and tetra-cyclic compounds utilising the thiadiazolopyrimidine ring system. The researchers also evaluated the antibacterial properties of these compounds. The results obtained in this study demonstrate the significant efficiencies of pyrano-thiadiazolopyrimidine compounds 8a–b and 9a–b against two strains of gram-positive bacteria, namely *S. aureus* and *B. cereus*. Additionally, the tetracyclic pyrazolopyrimido-thiadiazolopyrimidine derivatives 16a–b and 17a–b shown significant efficacy against both gram-negative bacterial strains, namely *Escherichia coli* and *Pseudomonas aeruginosa*. Furthermore, the compounds 8a–b and 9a–b exhibited significant efficacy against *Candida albicans*. The study evaluated the efficacy of recently developed thiadiazolopyrimidine-based compounds in inhibiting

the process of anti quorum sensing (anti-QS) in *C. violaceum* (Alqahtani, 2021).

The results indicated that derivatives 16a–b, 17a–b, 8b, and 9a had promising action in this regard. The MTT assay was used to evaluate the cytotoxic effects of these compounds on different cancer cell lines (MCF-7, PC3, Hep-2, and HepG2) as well as standard normal fibroblast cells (WI38). The derivatives 16a, 16b, 17a, and 17b, which belong to the pyrazolopyrimido-thiadiazolopyrimidine class, exhibited significant cytotoxic activity against MCF-7 cells, as evidenced by their IC50 values ranging from 5.69 to 9.36 µM. Furthermore, the validated structural activity relationship (SAR) of the investigated thiadiazolopyrimidine derivatives established a connection between the chemical composition and the effectiveness of their anticancer properties. In this study, in silico docking techniques were employed to investigate the inhibition of hormone signalling in breast tissue using the protein structure with the PDB code 5NQR. The findings were determined to be in accordance with the cytotoxic activity (Alqahtani, 2021).

In their study, El-Etrawy *et al*. employed a standard method to produce and synthesise a collection of thiouracil derivatives. These derivatives were deliberately designed to possess pharmacophoric characteristics that are essential for inhibiting thymidylate synthase (TS). Multiple methodologies were utilised to ascertain the chemical compositions of all synthesised compounds, including micro-elemental analyses and spectroscopic examinations. The potential of new thiouracil derivatives as anticancer and antibacterial drugs was evaluated in terms of their efficacy. The freshly synthesised compounds were subjected to *in vitro* screening against the MCF-7 cell line. The results of the investigation suggest that compounds 8, 11, 13a, and 12 exhibit a significant effect on the breast cancer cell line, as seen by their $IC_{50}$ values of 3.80, 4.00, 4.50, and 4.70 µg/ml, respectively, in comparison to doxorubicin. Furthermore, the researchers performed molecular docking analyses to propose putative mechanisms of action for the synthesised compounds and to interpret the observed anti-breast cancer benefits by specifically targeting thymidylate synthase. The study aimed to assess the antibacterial effectiveness of the newly developed compounds against three well-known strains: *Escherichia coli*, *Pseudomonas aeruginosa* (both classified as gram-negative bacteria), and Staphylococcus aureus (a gram-positive bacterium). The agar well diffusion method was employed for this evaluation. The findings derived from the evaluation of antibacterial activity revealed that a significant proportion of the compounds examined exhibited considerable levels of antibacterial efficacy (El-Etrawy & Sherbiny 2021).

The present study revealed that compounds 13a and 13b shown noteworthy antibacterial activity. The aforementioned compounds exhibited inhibitory zone values of 38 and 35 mm, correspondingly, when tested against Escherichia coli at a dose of 50 µg/ml. In a comparable manner, compounds 13a and 13b exhibited inhibition zone values of 25 and 23 mm, correspondingly, against Staphylococcus aureus when subjected to a concentration of 50 µg/ml. However, it was noted that all tested strains exhibited resistance to the synthesised compounds, with the exception of compound 7. Compound 7 exhibited remarkable activity in isolation against *Pseudomonas aeruginosa*, as evidenced by inhibition zone measurements of 22 mm at a dose of 50 µg/ml. Furthermore, a molecular docking analysis was performed to enhance comprehension of the binding mechanism exhibited by the most suitable molecules. The present study employed the crystal structure of the S. aureus DNA gyrase complex with ciprofloxacin for the purpose of analysis (El-Etrawy & Sherbiny 2021).

In their study, Atiya *et al*. (2022) successfully synthesised chalcone compounds with high to satisfactory yields. These compounds were utilised as effective intermediates for the synthesis of a diverse range of pyrimidine derivatives. The aforementioned derivatives were also synthesised with a high degree of efficiency. Pyrimidine derivatives exhibit elevated melting points, which can be attributed to their inherent stability. The biological activity of compounds (3-5), which are pyrimidine derivatives, was assessed for their antibacterial properties. Two types of bacteria, namely S. aureus (as the positive bacterial strain) and K. pneumonia (as the negative bacterial strain), were used for the evaluation. Three compounds exhibited biological action against the growth of *S. aureus*, and an increase in their concentration resulted in observed activity against *K. pneumonia*. Compound (4) does not exhibit biological action against the development of *S. aureus*, however it does demonstrate activity against the growth of *K. pneumonia*. Five compounds have demonstrated biological action against the growth of *S. aureus* and *K. pneumoniae* (Atiya *et al*., 2022).

Becan *et al*. successfully synthesised a set of novel 5-trifluoromethyl-2-thioxo-thiazolo[4,5-d]pyrimidines, denoted as 2a-e, using the cyclization process of 4-amino-2-thioxo-2,3-dihydro-3-substituted-1,3-thiazole-5-carboxamides with trifluoroacetic anhydride. The subsequent stage involved the chlorination of compounds 3a-e, resulting in the formation of the 7-chloro derivatives 3a-e. Furthermore, three 7-amino derivatives (4a-c) were synthesised through the reaction of compound 3b with methyl-, ethyl-, and fluorobenzylamine (Becan *et al*., 2022).

The antiproliferative capabilities of twelve compounds (2a-e, 3a-d, and 4a-c) were evaluated in biological investigations against human cancer cell lines (A375, C32, DU145, MCF-7/WT) as well as normal cell lines (CHO-K1 and HaCaT). Compounds 3a-3d and 4a shown a notable antiproliferative effect. The findings demonstrated a reduction in cellular populations subjected to treatment with compound 3b, suggesting that the compound impeded the multiplication of cancerous cells. Differential effects on proliferation were seen in normal human keratinocytes and hamster

ovarian cells, with varying degrees of reduction depending on the specific chemical. Furthermore, the study demonstrated that compounds 3a-3d, specifically those with a 7-chloro substitution, as well as compound 4a, which contains a short amino substituent, had enhanced efficacy against human prostate and melanoma cells. Notably, these compounds displayed a notable decrease in sensitivity towards normal fibroblasts. The enhanced efficacy of compounds 3a-3d relative to compounds 2a-2e could potentially be attributed to their higher lipophilicity and the incorporation of a highly electronegative substituent at position 7.

The National Cancer Institute selected four chemicals, namely 2b, 3b, 4b, and 4c, to be included in an anticancer screening panel consisting of about 60 human disease-oriented tumour cell lines. Out of the compounds that underwent screening, it was found that only 3b exhibited both cytostatic and cytotoxic effects, particularly against leukaemia and colon cancer cell lines (Becan *et al*., 2022).

Novel derivatives incorporating a trifluoromethyl moiety were synthesised in an effort to obtain bioactive molecules. The performed investigation revealed that the newly synthesised derivatives, namely 3a-3d and 4a, had significant activity, with compound 3b demonstrating particularly noteworthy results. Nevertheless, the incorporation of the trifluoromethyl group into the molecular framework of the novel thiazolo [4,5-d] pyrimidine derivatives did not yield a substantial enhancement in efficacy when compared to the derivatives containing heterocyclic or aromatic substituents. The efficacy of compound 3b is similar to that of its structural analogues. Collectively, the aforementioned data suggest that the recently formulated derivatives of 5-trifluoromethyl-2-thioxo-thiazolo[4,5-d]pyrimidine exhibit potential as viable candidates for future investigation and advancement as inhibitors in human cancer cells (Becan *et al*., 2022).

Othman *et al*. (2021) conducted a study in which they investigated the reaction between 2-methoxyaniline and chloroacetonitrile in ethanol. This reaction resulted in the formation of a crucial intermediate known as 2-((2-methoxyphenyl)amino) acetonitrile. The researchers then subjected this intermediate to further reactions with various aromatic aldehydes, such as benzaldehyde and/or 4-methylbenzaldehyde, in glacial acetic acid. These reactions yielded acrylonitrile derivatives. Subsequently, the acrylonitrile derivatives were reacted with urea and/or thiourea in refluxing ethanol, with the presence of a catalytic amount of HCl. This final step led to the synthesis of pyrimidine derivatives (Othman *et al*., 2021).

Synthesis of new pyrimidines 4a,b, 5a,b for use as tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR) was the primary goal of this study. Both human breast cancer MCF-7 cells and hepatocellular carcinoma HepG-2 cells were used to test the new compounds' cytotoxic potential. All of the newly discovered compounds demonstrated more cytotoxicity compared to erlotinib. Specifically, compound 4a exhibited higher potency than 5-fluorouracil, while the 4b counterpart showed similar efficacy to it. Compounds 4a and 4b were then tested for their inhibitory effects on kinases in connection to EGFRWT, EGFRL858R, and EGFRT790M. When compared to the reference drugs erlotinib and osimertinib, the pyrimidine analogues 4a and 4b showed much greater inhibitory activity against EGFRWT and its two mutant isoforms, EGFRL858R and EGFRT790M. Additionally, antibacterial testing was performed on all of the newly discovered analogues. When compared to the standard drugs gentamycin and ketoconazole, both 4a and 4b showed great promise in terms of broad-spectrum antibiotic action against the tested bacteria. Consistent with the results of the *in vitro* enzyme assay, docking results showed that compounds 4a and 4b had good binding interactions with EGFRWT and EGFRT790M. Additional in silico ADMET tests were performed to assess the novel compounds' oral bioavailability, drug-like properties, and possible toxicity concerns in humans (Othman *et al*., 2021).

Hassan *et al.* (2022) undertook an extensive investigation encompassing the synthesis of a range of 7-amino-pyrazolo[1,5-a]pyrimidines. The accomplishment was attained by a series of steps, commencing with the reaction between 5-amino-N-aryl-1H-pyrazole-4-carboxamides and 2-(arylidene)malononitriles in ethanol under reflux conditions. The first step resulted in the formation of an intermediate molecule, specifically the derivative (48) of 5-((2,2-dicyano-1-phenylethyl)amino)-1H-pyrazole. The intermediate under investigation possessed a cyclic imino group which shown nucleophilic characteristics, leading to its reaction with the cyano group resulting in the formation of derivatives of 7-imino-pyrazolo[1,5-a]pyrimidine-3-carboxamide. Following this, the displacement of protons and subsequent oxidation processes facilitated the synthesis of the ultimate products, namely the derivatives of 7-amino-pyrazolo[1,5-a]pyrimidine (Hassan *et al*., 2022).

A total of twenty compounds were synthesised, consisting of pyrazolo[1,5-a]pyrimidines (14a–j) and Schiff bases of pyrazole derivatives (16a–j). The antimicrobial activity of these compounds was assessed, and it was found that they exhibited varied degrees of inhibitory effects. It is worth mentioning that three pyrazolo[1,5-a]pyrimidines (14b, 14e, and 14j) and four pyrazole Schiff bases (16c, 16d, 16h, and 16i) exhibited a wide range of antimicrobial activity, as evidenced by inhibition zones of between 15 and 20 mm.

In addition to the aforementioned investigation, the study encompassed an analysis of the relationship between molecular structure and activity, as well as the development of predictive models for physicochemical qualities, drug-likeness, bioactivity, ADME (Absorption, Distribution, Metabolism, and Excretion), and toxicity. The present study involved conducting molecular docking simulations in silico, specifically targeting the active sites of crucial enzymes including

DNA gyrase and the secreted aspartic protease derived from C. albicans. The results of these simulations revealed encouraging binding affinities and the presence of numerous binding modes. The generation of electrostatic potential maps was performed in order to identify specific locations that had the potential for hydrogen bonding. This analysis provides additional support for the findings obtained from the docking investigation (Hassan *et al*., 2022).

In their study, Pan *et al* conducted the synthesis of 20 new derivatives of 1,3,4-thiadiazole that incorporated a pyrimidine skeleton. These compounds were subsequently evaluated for their *in vitro* antifungal properties. The synthesised compounds exhibited superior antifungal efficacy in comparison to pyrimethanil, as evidenced by the results obtained from bioassays. Hence, the utilisation of 1,3,4-thiadiazole derivatives incorporating a pyrimidine framework presents a promising avenue for the identification of novel fungicidal drugs (Pan *et al*., 2022).

The objective of Khedr *et al*. (2021) study was to tackle the persistent issue in the field of drug development, which involves overcoming chemotherapeutic resistance in cancer cells. The researchers directed their attention towards the synthesis of a novel category of artificial chemicals referred to as thienopyrimidine analogues (1–9). These compounds were specifically developed to function as inhibitors of mGluR-1, a therapeutic target, and were anticipated to possess potential anticancer effects. The investigators performed in-vitro tests utilising different cancer cell lines, namely MCF-7, A-549, and PC-3, and juxtaposed the findings with those obtained from a normal cell line, WI-38. The thienopyrimidine analogues demonstrated diverse levels of anticancer efficacy, while compound 7b had the highest potency against all three cancer cell lines. Significantly, it performed better than conventional chemotherapeutic agents such as Doxorubicin and 5-Fluorouracil.

Subsequent inquiries unveiled that compound 7b exhibited a notable reduction in the release of extracellular glutamate and prompted the initiation of early apoptosis in cancerous cells. At the level of gene expression, there was an upregulation of apoptotic genes and a downregulation of anti-apoptotic genes. The compound's robust binding and stability were further validated using molecular docking studies, indicating its promise as a viable candidate for the creation of a mGluR inhibitor with anticancer properties. Consequently, it is imperative to conduct future in-vivo and clinical investigations to explore its efficacy and safety (Khedr *et al*., 2021).

The study undertaken by Haffez *et al*. (2020) was centred upon the synthesis and assessment of novel compounds, namely 6-amino-5-cyano-4-aryl-2-mercaptopyrimidines and condensed pyrimidine analogues. The primary objective of this research was to investigate the potential of these compounds as anticancer agents. The synthesis of these compounds was carried out via a one-pot condensation technique, wherein p-nitrobenzaldehyde or p-anisaldehyde, malononitrile, and thiourea were employed. This process led to the formation of a sequence of compounds known as 6-amino-5-cyano-4-aryl-2-mercaptopyrimidines (1-9a,b). The pyrimidine analogues that were synthesised were subsequently exposed to in-vitro screening against HepG2 and MCF-7 cancer cell lines, in comparison to normal WI-38 cells.

Drug 8a demonstrated significant antiproliferative action against MCF-7 cells, as evidenced by its IC50 value of 12.9 µM. In contrast, this drug exhibited low cytotoxicity on normal WI-38 cells, with an IC50 value above 100 µM. Moreover, compound 8a exhibited the capacity to initiate apoptosis at an early stage, halt the cell cycle, and upregulate the expression of particular genes linked to apoptosis. The results of molecular docking experiments suggest that the compound has the ability to effectively suppress the activity of phosphodiesterases, specifically PDE4B. In light of the aforementioned results, it can be inferred that compound 8a exhibits considerable potential as a prospective agent for combating cancer, therefore justifying the need for additional research and advancement in this area (Haffez *et al*., 2020).

Table 1 provides a summary of key references, including reference numbers, compound types, activities, and findings.

**Table 1: Summary of Pyrimidine Derivative Studies and Activities.**

| Compound Type | Activities | Findings | References |
|---|---|---|---|
| Pyrido thienopyrimidine Derivatives | Antimicrobial, Anticancer | Compounds 6c, 8b, 9a, and 9b: Significant antimicrobial activity (MIC values: 4-16 µg/mL). Compounds 2b, 4a, 6a, 7b, 7c, and 9a: Strong anticancer activity. Compounds 6a, 7b, 7c, and 9a showed potential mechanisms of action. | (El-Deen *et al*., 2022) |
| Diverse Pyrimidines | Anticancer | Compounds 3b and 3d: Promising anti-proliferative activity against prostate carcinoma PC3 cells, outperforming vinblastine sulfate. Compounds 3b, 3f, 3g, 3h, and 5: Enhanced safety and selectivity compared to vinblastine sulfate. Adherence to Lipinski's Rule of Five for potential oral bioavailability. Compound 3b demonstrated potent anticancer activity and selectivity | (El-Atawy *et al*., 2022) |

| | | | |
|---|---|---|---|
| | | towards cancer cells, possibly through interaction with Bcl-2. | |
| N-(4-(Substituted Amino) Thieno[2,3-d]pyrimidin-2-yl) Thiophene/Furan-2-carboxamide Derivatives | Antimicrobial, Anticancer | Mild synthesis process with satisfactory yields. Compounds 8j, 8i, 8h, and 8g: Notable antimicrobial activity. Compounds 2a, 2b, 11a, and 11b: Potent anticancer activity with potential mechanisms of action. | (Prabhakar *et al*., 2017) |
| Pyrimidine Derivatives | Antimicrobial | Significant antimicrobial activity against Gram-positive and Gram-negative bacteria, as well as fungal strains. Compounds 2, 5, 10, 11, and 12 showed promising activity, outperforming standard drugs. Electron-withdrawing groups enhanced antimicrobial potential. | (Narwal *et al*., 2017) |
| Fused Pyrimidine Derivatives | Antibacterial, Antifungal, Anticancer | Compound 14b: Most active against Candida albicans. Compound 8c: Highest MIC against S. aureus and E. coli. Compound 11c: Most active against B. subtilis. Compound 7: Most active against various cancer cell lines. | (Shaaban *et al*., 2018) |
| Azo-Pyrimidine Derivatives | Antibacterial | Compound 31: Most active against Gram-positive and Gram-negative bacteria. Thiopyrimidine ring broadened antibacterial spectrum. | (Abdelgawad, 2019) |
| 2,4-Disubstituted-6-Thiophenyl-Pyrimidine Derivatives | Antibacterial | Compound 33: Effective against MRSA and VRE, outperforming methicillin and vancomycin. Inhibited ATPase activity and Fts Z polymerization. Demonstrated resistance generation in methicillin-resistant *S. aureus*. | (Fang *et al*., 2019) |
| 2-Phenylpyrimidine Coumarin Derivatives | Anticancer | Most derivatives inhibited tumor cell proliferation effectively. Compound B32 showed promising antiproliferative activity, comparable to the gold standard drug. | (Lv *et al*., 2017) |
| Pyrazolo[1,5-a]pyrimidine Derivatives | Antibacterial, Antifungal | All compounds tested for antimicrobial activity. Compounds 7b, 7c, 14a, 14b, 14e, and 14i: High docking scores for inhibiting RNA polymerase. Compound 7b effectively inhibited RNA polymerase. | (Abdallah & Galal 2018) |
| Pyrimidine Derivatives | Antibacterial | Compounds 10 and 11: Significant antibacterial activity. Compounds 5, 6, and 8: Moderate to excellent antibacterial activity. Compounds 5, 6, and 10: Significant antifungal activity against *Penicillium funiculosum*. Compounds 7 and 8: Moderate antifungal activity against *Aspergillus niger*. | (Bhagchand, 2019) |
| 1,3,4-Thiadiazole Derivatives | Antifungal | Moderate to good antifungal activities against various fungi, including *P. infestans* and *G. zeae*. Significant inhibition rates against *G. zeae*. | (Chen *et al*., 2021) |
| Various Derivatives (Tri- and Tetra-cyclic) | Antibacterial & Anticancer | Antibacterial efficacy against gram-positive and gram-negative bacteria, as well as *Candida albicans*. Anticancer potential against different cancer cell lines. Inhibition of antiquorum sensing in *C. violaceum*. | (Alqahtani, 2021) |
| Thiouracil Derivatives | Antibacterial & Anticancer | Antibacterial effectiveness against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Significant anticancer activity against breast cancer cell line MCF-7. | (El-Etrawy & Sherbiny 2021) |

| | | | |
|---|---|---|---|
| Pyrimidine Derivatives | Antibacterial | Antibacterial activity against *S. aureus* and *K. pneumonia*. Biological action against the growth of *S. aureus* and *K. pneumoniae*. | (Atiya *et al*., 2022) |
| Thiazolo[4,5-d]pyrimidine Derivatives | Anticancer | Antiproliferative effects on various cancer cell lines, especially human prostate and melanoma cells. Cytostatic and cytotoxic effects against leukaemia and colon cancer cell lines. | (Becan *et al*., 2022) |
| Pyrimidine Derivatives | Anticancer & Antibacterial | Cytotoxicity against MCF-7 and HepG-2 cancer cells. Broad-spectrum antibiotic action against tested microorganisms. | (Othman *et al*., 2021) |
| Pyrazolo[1,5-a]pyrimidines | Antimicrobial | Varied antimicrobial effects. Molecular docking and electrostatic potential mapping for binding interactions. | (Hassan *et al*., 2022) |
| 1,3,4-Thiadiazole Derivatives | Antifungal | Superior antifungal efficacy compared to pyrimethanil. | (Pan *et al*., 2022) |
| Thienopyrimidine Analogues | Anticancer | Anticancer efficacy against MCF-7, A-549, and PC-3 cancer cell lines. Potential as mGluR inhibitors. | (Khedr *et al*., 2021) |
| 6-Amino-5-cyano-4-aryl-2-mercaptopyrimidines | Anticancer | Significant antiproliferative action against MCF-7 cells. Cytotoxicity selective for cancer cells | (Haffez *et al*., 2020) |

## DISCUSSION

The studies discussed in the provided text collectively present a compelling overview of the diverse pharmacological potential of pyrimidine-based compounds, spanning from their applications in cancer therapy to their antimicrobial properties. The synthesis and evaluation of these compounds have shed light on their efficacy and mechanisms of action, opening up exciting avenues for future research and drug development.

### *A. Pyrimidine Derivatives: A Ray of Hope*

Pyrimidine derivatives have shown promise not only as antimicrobial agents but also as potential anticancer therapeutics. Novel synthetic methods for preparing pyrazolopyrimidine derivatives have opened up new possibilities in the fight against cancer and infectious diseases. The studies by El-Deen, El-Atawy, Prabhakar, Narwal, and Shaaban, all highlight the antimicrobial potential of pyrimidine derivatives, showcasing their ability to outperform standard drugs and the critical role of electron-withdrawing groups in enhancing their efficacy. These compounds could be crucial in addressing the global health challenge of antimicrobial resistance.

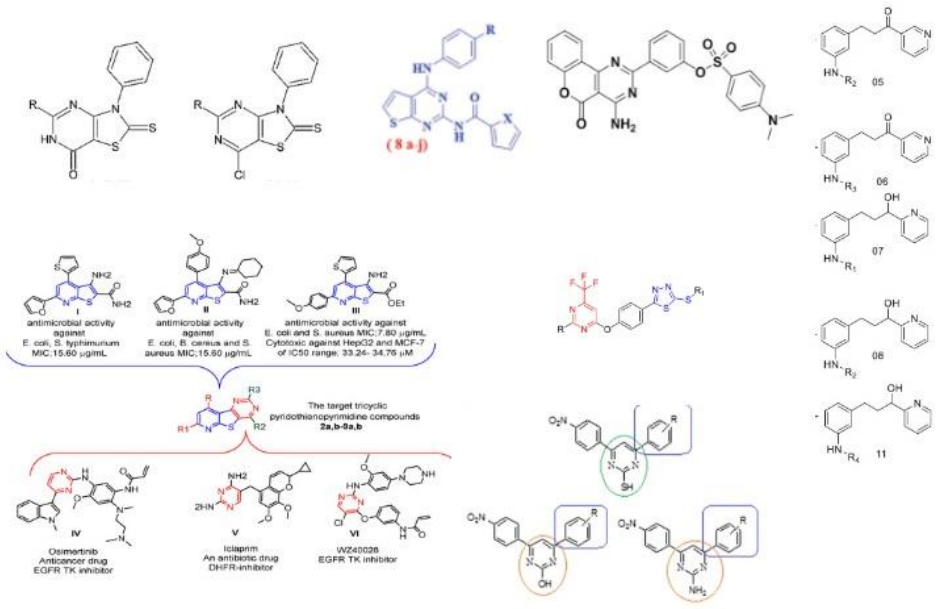


**Fig. 3.** Examples of Structures Depicting the Chemical Diversity of Pyrimidine Derivatives.

*B. Antimicrobials: A Multifaceted Approach*

Antimicrobial compounds derived from pyrimidines encompass a wide range of agents, from antifolates to sulfa drugs. These compounds exhibit antagonistic effects against various pathogens, demonstrating their versatility in combating infectious diseases. For instance, Brodiprim and Iclaprim have showcased their antibacterial prowess, even against drug-resistant strains. These findings emphasize the ongoing need for innovative antimicrobial agents, especially in the face of antibiotic resistance.

Several studies investigated the antibacterial and antifungal properties of pyrimidine derivatives. These findings highlight the potential of pyrimidine derivatives as antimicrobial agents. The variations in antibacterial and antifungal activities across different compounds suggest a structure-activity relationship (SAR) that could guide the design of more potent derivatives for future studies.

*C. Pyrimidine-Based Compounds in Cancer Therapy*

Erlotinib, a pyrimidine-based anticancer medication, has gained recognition for its effectiveness in treating pancreatic cancer and non-small cell lung cancer (NSCLC). Its approval by the Food and Drug Administration (FDA) underscores the significance of pyrimidine derivatives in modern cancer therapy. Pyrimidines like Erlotinib, acting as platelet-derived growth factor antagonists and phosphodiesterase inhibitors, target specific cellular pathways critical for cancer progression. This highlights the importance of pyrimidine-based compounds in precision medicine and the evolving landscape of oncology.

In the realm of cancer therapy, pyrimidine-based compounds have exhibited significant anticancer potential. El-Deen's study, in particular, underscores the promise of select compounds in combating cancer, especially through inhibition of the EGFRWT enzyme. Furthermore, El-Atawy's research identifies pyrimidine-based compounds with potent anti-proliferative activity against prostate carcinoma cells, offering new possibilities for targeted cancer treatments. The discovery of these compounds, adhering to Lipinski's Rule of Five, suggests the potential for oral bioavailability, further enhancing their therapeutic applicability.

*E. Exploring Mechanisms of Action, Molecular Docking and Structure-Activity Relationship (SAR)*

Molecular docking studies were performed in several studies to understand the binding interactions between compounds and their target proteins/enzymes. These analyses provided insights into the compounds' binding affinity and stability, further supporting their potential as therapeutic agents. SAR analyses also revealed the importance of specific chemical groups or substituents in enhancing the compounds' bioactivity.

Several studies delve into the mechanisms of action of pyrimidine-based compounds. Molecular docking simulations and *in vitro* assays provide valuable insights into how these compounds interact with their molecular targets. For instance, Lv *et al*. (2017) demonstrate the potential of 2-phenylpyrimidine coumarin derivatives in inhibiting tumor cell proliferation by interfering with specific cellular processes. Similarly, Fang *et al*. (2019) highlight the inhibitory effects of Compound 33 on bacterial cell division through interaction with the GTP binding site of Fts Z, thus offering a potential solution to antibiotic-resistant bacteria.

The studies shed light on the potential mechanisms of action for these compounds. They were found to impact various cellular processes, including apoptosis and cell cycle regulation. Moreover, the compounds exhibited selective cytotoxicity against cancer cells while sparing normal cells, a critical feature for potential anticancer drugs. These mechanisms of action need further exploration for a comprehensive understanding.

## CONCLUSIONS

The field of medical chemistry is centred around the research and synthesis of medicinal chemicals or pharmaceutical agents that possess beneficial properties for the enhancement of human health and overall well-being. Approximately 50% of contemporary organic chemistry research is dedicated to the investigation of heterocyclic compounds, which have demonstrated significant use as medicinal agents, exhibiting both broad applicability and economic viability. Pyrimidines, a prominent class of heterocyclic compounds, are widely recognised for their significant pharmacological effects. Lipids are integral components of cellular structures and play a crucial role in all forms of organic life. Their biological functions are vital for the advancement and dissemination of efficacious novel pharmaceuticals.

Anticonvulsant, antibacterial, antifungal, antiviral, and anticancer properties are just some of the many biological and pharmacological activities displayed by pyrimidine and its derivatives. The synthetic flexibility of pyrimidine has allowed for the generation of a large number of structurally diverse derivatives, which has facilitated the study of a wide range of biochemical targets. The biological functions of the pyrimidine scaffold have been described in this article. Given the pyrimidine's biological activities, the medicinal chemist will likely continue to be interested in the pyrimidine skeleton for use in medicinal chemistry and drug development; therefore, it is crucial that effective and reliable methods be developed for the construction of these molecules. The pyrimidine scaffold's anticancer and antimicrobial properties have been outlined in this review. This manuscript's scientific findings could be useful in inspiring future researchers to investigate this heterocyclic scaffold. A potential outcome of this review article is attracting researchers interested in the structural design and development of novel active pyrimidine scaffolds with increased activity and decreased toxicity.

## FUTURE SCOPE

In conclusion, the research on pyrimidine-based compounds discussed in this text signifies their multifaceted potential in both cancer therapy and antimicrobial applications. These studies lay the

foundation for further investigations into the development of novel drugs, mechanisms of action, and potential clinical applications. The remarkable antimicrobial and anticancer properties displayed by specific compounds highlight their importance in addressing some of the most pressing challenges in healthcare today, from drug-resistant infections to cancer treatment. As research in this field continues to advance, pyrimidine-based compounds hold significant promise for the future of medicine and the improvement of patient care.

The findings from these studies collectively suggest that pyrimidine derivatives and related compounds hold promise as potential drug candidates for a range of therapeutic applications, from antimicrobial to anticancer treatments. However, further research is needed to validate their efficacy *in vivo* and to assess their safety profiles.

In conclusion, the synthesis and evaluation of pyrimidine derivatives and related compounds have yielded compounds with significant potential for various biomedical applications. These studies provide a foundation for future research aimed at developing novel drugs with enhanced efficacy and safety profiles. Moreover, the structure-activity relationships and mechanisms of action identified in these studies can serve as valuable insights for the rational design of new compounds with optimized therapeutic properties.

**Acknowledgement.** The authors are grateful to the Principal Prof. Anna Pratima Nikalje and Wilson College management for providing research laboratory facilities. We express a deep sense of gratitude to Dr. Abhijeet Kadam Department of Chemistry, John Wilson Education Society's, Wilson College (Autonomous), Mumbai, 400007, Maharashtra, India, for his assistance and providing the valuable suggestions and support.

**Conflict of Interest.** None.

## REFERENCES

Abdallah, A. E. M., and Galal H. E. (2018). Design, synthesis, docking, and antimicrobial evaluation of some novel pyrazolo [1,5-a] pyrimidines and their corresponding cycloalkane ring-fused derivatives as purine analogs. *Drug Des Devel Ther., 12,* 1785-1798.

Abdelgawad, M. A. (2019). Synthesis and antibacterial evaluation of new azo-pyrimidine derivatives. *J Appl Pharm Sci., 9*(1), 9-16

Ali, K. A., Ragab, E. A., Farghaly, T. A., and Abdalla, M. M. (2011). Synthesis of new functionalized 3-substituted [1,2,4]triazolo[4,3-a]pyrimidine derivatives: Potential antihypertensive agents. *Acta Pol. Pharm., 68,* 237–247.

Alqahtani, A. M. (2021). Synthesis and biological screening of new thiadiazolopyrimidine-based polycyclic compounds. *Scientific Reports, 11*(1), 15750.

Atiya, R. N., Salih, N. A., and Adam, R. W. (2022). Preparation with Biological Study for Pyrimidine Derivatives from Chalcone. *Int J Drug Deliv Technol, 12*(1), 174-179.

Avupati, D. V. R., and Yejella, P. R. P. (2014). A review on pyrimidine scaffold. *World J Pharm Res Technol, 3*(10), 1563–1587.

Becan, L., Pyra, A., Rembiałkowska, N., and Bryndal, I. (2022). Synthesis, Structural Characterization and Anticancer Activity of New 5-Trifluoromethyl-2-thioxo-thiazolo [4, 5-d] pyrimidine Derivatives. *Pharmaceuticals, 15*(1), 92.

Bhagchand, J. (2019). Prasanta Kumar Santra Synthesis and Evaluation of Antimicrobial Activity of Pyrimidine Derivatives. *Asian J. Pharm. Clin. Res., 12,* 156-163.

Cassir, N., Rolain, J.M., and Brouqui, P. (2014). A new strategy to fight antimicrobial resistance: the revival of old antibiotics. *Front Microbiol., 5,* 551.

Chen, M., Zhang, X., Lu, D., Luo, H., Zhou, Z., Qin, X., Wu, W., and Zhang, G. (2021). Synthesis and bioactivities of novel 1, 3, 4-thiadiazole derivatives of glucosides. *Frontiers in Chemistry, 9,* 645876.

Chen, Q., Zhu, X. L., Jiang, L.L., Liu, Z. M., and Yang, G. F. (2008). Synthesis, antifungal activity and CoMFA analysis of novel 1,2,4- triazolo[1,5-a]pyrimidine derivatives, *Eur. J. Med. Chem,* (43), 595–603.

El-Atawy, M. A., Alshaye, N. A., Elrubi, N., Hamed, E. A., & Omar, A. Z. (2022). Pyrimidines-Based Heterocyclic Compounds: Synthesis, Cytoxicity Evaluation and Molecular Docking. *Molecules, 27*(15), 4912.

El-Deen, E. M. M., Anwar, M. M., Abd El-Gwaad, A. A., Karam, E. A., El-Ashrey, M. K., and Kassab, R. R. (2022). Design and synthesis of some novel pyridothienopyrimidine derivatives and their biological evaluation as antimicrobial and anticancer agents targeting EGFR enzyme. *Arabian Journal of Chemistry, 15*(4), 103751.

El-Etrawy, A. A. S., and Sherbiny, F. F. (2021). Design, synthesis, biological assessment and molecular docking studies of some new 2-Thioxo-2, 3-dihydropyrimidin-4 (1*H*)-ones as potential anticancer and antibacterial agents. *Journal of Molecular Structure, 1225,* 129014.

Elgemeie, G. H., Abu-Zaied, M., Hebishy, A., Abbas, N., and Hamed, M. (2016). A first microwave-assisted synthesis of a new class of purine and guanine thioglycoside analogs. *Nucleosides Nucleotides Nucleic Acids, 35*(9), 459–478.

Elgemeie, G. H., Abu-Zaied, M. A., and Loutfy, S. A. (2017). 4-Aminoantipyrine in carbohydrate research: design, synthesis and anticancer activity of a novel class of derivatives of 4-aminoantipyrine thioglycosides and their corresponding pyrazolopyrimidine and pyrazolopyridine thioglycosides. *Tetrahedron, 73,* 5853–5861.

Fandzloch, M., and Lakomska, I. (2018). New Dimethyl Sulfoxide Ruthenium(III) Complex with 5,7-di-tert-butyl[1,2,4]triazolo[1,5- a]pyrimidine and Method for production thereof. *PL229322B1, 31 July 2018.*

Fang, Z., Zheng, S., Chan, K.F., Yuan, W., Guo, Q., and Wu, W. (2019). Design, synthesis and antibacterial evaluation of 2,4- disubstituted-6-thiophenyl-pyrimidines. *Eur J Med Chem., 161,*141-153.

Gajera, S. B., Mehta, J. V., and Patel, M. N. (2016). Design of Multifunctional Iridium III Compounds as a Potential Therapeutic Agents from Basic Molecular Scaffolds, *Chem. Sel., 1,* 3966–3973.

Goossens, H., Ferech, M., Vander Stichele, R., and Elseviers, M. (2005). Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet. 365*(9459), 579–587.

Guan, L. P., Sui, X., Chang, Y., Yan, Z. S., Tong, G. Z. and Qu, Y. L. (2012). Design, synthesis and anticonvulsant activity evaluation of 7-substituted -[1,2,4]-triazolo[4,3-f]pyrimidine derivatives. *Med. Chem. 8,* 1076–1083.

Gupta, Y., Gupta, V., and Singh, S. (2013). Synthesis, characterization and antimicrobial activity of

pyrimidine based derivatives. *J Pharm Res, 7*, 491–495.

Haffez, H., Taha, H., Rabie, M. A., Awad, S. M., and Zohny, Y. M. (2020). Synthesis, biological evaluation and molecular docking studies of novel thiopyrimidine analogue as apoptotic agent with potential anticancer activity. *Bioorganic Chemistry, 104*, 104249.

Hassan, A. S., Morsy, N. M., Awad, H. M., and Ragab, A. (2022). Synthesis, molecular docking, and in silico ADME prediction of some fused pyrazolo [1, 5-a] pyrimidine and pyrazole derivatives as potential antimicrobial agents. *Journal of the Iranian Chemical Society, 19*(2), 521-545.

Hawser, S., Lociuro, S., and Islam, K. (2006). Dihydrofolate reductase inhibitors as antibacterial agents. *Biochem Pharmacol., 71*(7), 941–948.

Khedr, M. A., Abu-Zied, K. M., Zaghary, W. A., Aly, A. S., Shouman, D. N., and Haffez, H. (2021). Novel thienopyrimidine analogues as potential metabotropic glutamate receptors inhibitors and anticancer activity: Synthesis, *In-vitro*, *In-silico*, and SAR approaches. *Bioorganic Chemistry, 109*, 104729.

Khobragade, C. N., Bodade, R.G., Konda, S. G., Dawane, B.S., and Manwar, A. V. (2010). Synthesis and antimicrobial activity of novel pyrazolo[3,4-d]pyrimidin derivatives. *Eur J Med Chem. 45*(4), 1635–1638.

Lakomska, I., Jakubowski, M., Barwiolek, M., and Muziol, T. (2019). Different bonding of triazolopyrimidine to platinum(IV). Structural and *in vitro* cytotoxicity studies. *Polyhedron, 160*, 123–129.

Lotinun, S., Sibonga, J. D., and Turner, R. T. (2003). Triazolopyrimidine (trapidil), a platelet-derived growth factor antagonist, inhibits parathyroid bone disease in an animal model for chronic hyperparathyroidism. *Endocrinology, 144*(5), 2000-2007.

Lv, N., Sun, M., Liu, C., and Li, J. (2017). Design and synthesis of 2-phenylpyrimidine coumarin derivatives as anticancer agents. *Bioorg Med Chem Lett 27*, 4578–4581.

Ma, Y. C., Yu, Y. H., Hou, G. F., Huang, J. H., and Gao, J. S. (2016). Synthesis, crystal structure and herbicidal activity of a series of [1,2,4]triazolo[1,5-a]pyrimidine-2-sulfonamide compounds, *Heterocycles, 92*, 829–843.

Marinescu, M. (2021). Biginelli reaction mediated synthesis of antimicrobial pyrimidine derivatives and their therapeutic properties. *Molecules, 26*(19), 6022.

Meneghesso, S., Vanderlinden, E., Stevaert, A., McGuigan, C., Balzarini, J., and Naesens, L., (2012). Synthesis and biological evaluation of pyrimidine nucleoside monophosphate prodrugs targeted against influenza virus. *Antiviral research, 94*(1), 35-43.

Miller, K. D., Nogueira, L., Mariotto, A. B., Rowland, J. H., Yabroff, K. R., Alfano, C. M., Jemal, A., Kramer, J.L., and Siegel, R. L. (2019). Cancer treatment and survivorship statistics. *CA: a cancer journal for clinicians, 69*(5), 363-385.

Mishra, R.P., Oviedo-Orta, E., Prachi, P., Rappuoli, R., and Bagnoli, F. (2012). Vaccines and antibiotic resistance. *Curr. Opin Microbiol, 15*(5), 596–602.

Mitra, B., and Ghosh, P. (2021). Copper catalysis for pyrazines and quinoxalines. *In Copper in N-Heterocyclic Chemistry*, 221-248.

Moradivalikboni, R., Asadzadeh, S. T., Baghernejad, M., Heidarnezhad, Z., and Alinezhad, H. (2015a). Reaction 2-Benzyl 5-Oxo 5-H 6-Ethyl carboxylate 7-phenyl -1,3,4-thiadiazolo- [3,2-a]- pyrimidine with Amin derivatives and study of Biological properties. *Biological Forum – An International Journal, 7*(1), 152-158.

Moradivalikboni, R., Heidarnezhad, Z., Alinezhad, H., Tavakkoli, S. M., and Heidarnezhad, F. (2015b). Synthesis of 2-R 5-oxo5-H6- N-ethylcarboxamide7-phenyl-[1,3,4]thiadiazolo-[3,2-a]pyrimidine and 2-R 5-oxo5-H6- N-methylcarboxamide 7-phenyl-[1,3,4]thiadiazolo-[3,2-a]pyrimidine and Biological properties. *Biological Forum – An International Journal 7*(1), 741-748.

Nagender, P., Reddy, G. M., Kumar, R.N., Poornachandra, Y., Kumar, C. G. and Narsaiah, B. (2014). Synthesis, cytotoxicity, antimicrobial and anti-bioflm activities of novel pyrazolo[3,4-b] pyridine and pyrimidine functionalized 1,2,3-triazole derivatives. *Bioorg Med Chem Lett 24*, 2905–2908.

Narwal, S., Kumar, S., and Verma, P. K. (2017). Design, synthesis and antimicrobial evaluation of pyrimidin-2-ol/thiol/amine analogues. *Chemistry Central Journal, 11*, 1-9.

Nettekoven, M., Adam, J. M., Bendels, S., Bissantz, C., Fingerle, J., Grether, U., Gruener, S., Guba, W., Kimbara, A., and Ottaviani, G. (2016). Novel triazolopyrimidine-derived cannabinoid receptor 2 agonists as potential treatment for inflammatory kidney diseases, *Chem Med Chem, 11*, 179–189.

Othman, I. M., Alamshany, Z. M., Tashkandi, N. Y., Gad-Elkareem, M. A., Anwar, M. M., and Nossier, E. S. (2021). New pyrimidine and pyrazole-based compounds as potential EGFR inhibitors: Synthesis, anticancer, antimicrobial evaluation and computational studies. *Bioorganic Chemistry, 114*, 105078.

Pan, N., Liu, C., Wu, R., Fei, Q., and Wu, W. (2022). Novel pyrimidine derivatives bearing a 1, 3, 4-thiadiazole skeleton: Design, synthesis, and antifungal activity. *Frontiers in Chemistry, 10*, 922813.

Prabhakar, V., Babu, K. S., Ravindranath, L. K., and Latha, J. (2017). Design, synthesis, characterization and biological activity of novel thieno [2, 3-d] pyrimidine derivatives. *Indian J. Adv. Chem. Sci, 5*(1), 30-42.

Ramirez-Macias, I., Maldonado, C. R., Marin, C., Olmo, F., Gutierrez-Sanchez, R., Rosales, M. J., Quiros, M., Salas, J.M., and Sanchez- Moreno, M. (2012). *In vitro* anti-leishmania evaluation of nickel complexes with a triazolopyrimidine derivative against Leishmania infantum and Leishmania braziliensis. *J. Inorg. Biochem., 112*, 1–9.

Sader, H. S., Fritsche, T. R., and Jones, R. N. (2009). Potency and bactericidal activity of iclaprim against recent clinical gram-positive isolates. *Antimicrob Agents Chemother. 53*(5), 2171–2175.

Selvam, T. P., James, C. R., Dniandev, P. V., & Valzita, S. K. (2015). A mini review of pyrimidine and fused pyrimidine marketed drugs. *Research in Pharmacy, 2*(4), 1-9.

Shaaban, M. A., Mohamed, K. O., Hegazi, M. E., Shaykoon, M. A., and Elshaier Y. A. M. M. (2018). Synthesis of Some Pyrimidine and Fused Pyrimidine Derivatives with Antimicrobial and Anticancer Activities. *Der Pharma Chemica, 10*(7), 180-200.

Shahi, M. N., Perveen, N., Khan, M. N., Khakwani, S., and Khan, M. A. (2016). Triazolopyrimidines: Synthesis of aryl-1,2,4-triazolo[1,5- a]pyrimidines by Doebner-Miller reaction and their antibacterial activity. *Asian J. Chem. 28*, 2665–2669.

Tiwari, K. N., and Jayanti Singh, J. (2009). Effective Organogenesis from Different Explants of *Bacopa*

*monniera* L. (Wettst.)-An Important Medicinal Plant. *Biological Forum — An International Journal, 1*(2), 20-25.

Van Roosbroeck, Y. E. M., Buijnsters, P. J. J. A., Tresadern, G., Jacoby, E., Oehlrich, D., and Gijsen, H. J. M. (2018). [1,2,4] Triazolo[1,5-a] pyrimidine Compounds as PDE2 Inhibitors and their Preparation. *WO2018083103A1,* 11 May 2018.

Wisniewska, J., Fandzloch, M., and Lakomska, I. (2019). The reduction of ruthenium(III) complexes with triazolopyrimidine ligands by ascorbic acid and mechanistic insight into their action in anticancer therapy. *Inorg. Chim. Acta, 484,* 305–310.

Zhang, Z., Xie, J., Zhu, M., Xue, D., and Liu, Q. (2010). Diaryl-1,2,4-triazolo[4,3-a]pyrimidine Heterocyclic Compounds and Their Preparation, Pharmaceutical Compositions and Use in the Treatment of Vascular Diseases and Hypertension. CN101735221A.

Zuniga, E. S., Korkegian, A., Mullen, S., Odingo, J., Hembre, E. J., Cortez, G., Cramer, J., Masquelin, T., Hipskind, P. A., and Ornstein, P. L. (2017). The synthesis and evaluation of triazolopyrimidines as anti-tubercular agents. *Bioorg. Med. Chem. 25,* 3922–3946.

**How to cite this article:** Ajay A. Kumbhar, Harichandra A. Parbat and Anna Pratima Nikalje (2023). Exploring the Potential of Pyrimidine: A Comprehensive Review of its Biological Roles, Medicinal Applications, and Synthetic Methodologies in Drug Development. *Biological Forum – An International Journal*, *15*(4): 963-976.