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(REVIEW ARTICLE)

Pyrimidine derivatives: Recent discoveries and development towards its medicinal impact

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Abstract

Pyrimidine derivatives' many biological functions and possible therapeutic uses have attracted a lot of research in the field of medicinal chemistry. Recent developments in the synthesis, biological assessment, and therapeutic uses of molecules based on pyrimidines are highlighted in this review. The significance of pyrimidine derivatives in treating a range of ailments, including cancer, infectious diseases, and metabolic disorders, is discussed, along with innovative synthesis approaches and important pharmacological findings. In order to give a thorough picture of the present status of pyrimidine derivative research and its implications for upcoming medication development, this review will analyze recent literature and case studies.

Keywords: Pyrimidine; Anticancer Activities; Heterocyclic; Antimicrobial activity; Antitumor activity

1. Introduction

Considering heterocyclic compounds have a wide range of molecular structures, they are frequently used in the pharmaceutical medical industry. The biological potential of pyrimidine (Fig. 1) and its derivatives is widely recognized, owing to their varied nature. With nitrogen atoms at positions 1 and 3, pyrimidines are six-membered unsaturated rings made of carbon and nitrogen that are found in nature in a variety of forms with improved biological potential, such as antihypertensive, anticancer, antimicrobial, anti-inflammatory, antioxidant, etc. [1]. Thymine, cytosine, and uracil are the three pyrimidines that are most prevalent. The most often recognized pyrimidine bases are those found in DNA and RNA, and because they are a part of nucleic acid, pyrimidines have a special place in chemistry. Pyrimidine serves as a raw material for the synthesis of many different heterocyclic compounds and as a parent substance for the production of drugs. Pyrimidines, sometimes referred to as 1,3-diazone or m-diazine, are classified as cyclic amines [2]. In addition to being used to treat leukemia, many pyrimidine derivatives are also employed in the synthesis of other substituted pyrimidines and in the manufacture of thyroid medications [3]. In addition, they have anticancer, herbicidal, and plant growth regulating properties [4].

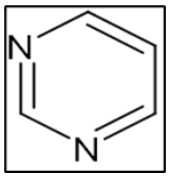

Figure 1 Pyrimidine.

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The breakdown products of uric acid were referred to as pyrimidines, or "m-diazine." By oxidizing uric acid with nitric acid in 1818, Brugnatelli produced alloxan (5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione) (Fig. 2), the first pyrimidine derivative to be isolated [5]. Pyrimidine has three distinct pairings of bond lengths and four distinct bond angles, with one axis of symmetry centered at the 2–5 axis. As a result, three distinct chemical shifts can be identified in the 1 H and 13C nuclei in the 1 H and 13CNMR signals. Unequal replacement at positions 4 or and 6 results in the loss of symmetry [6].

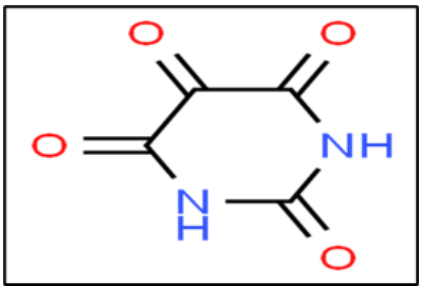


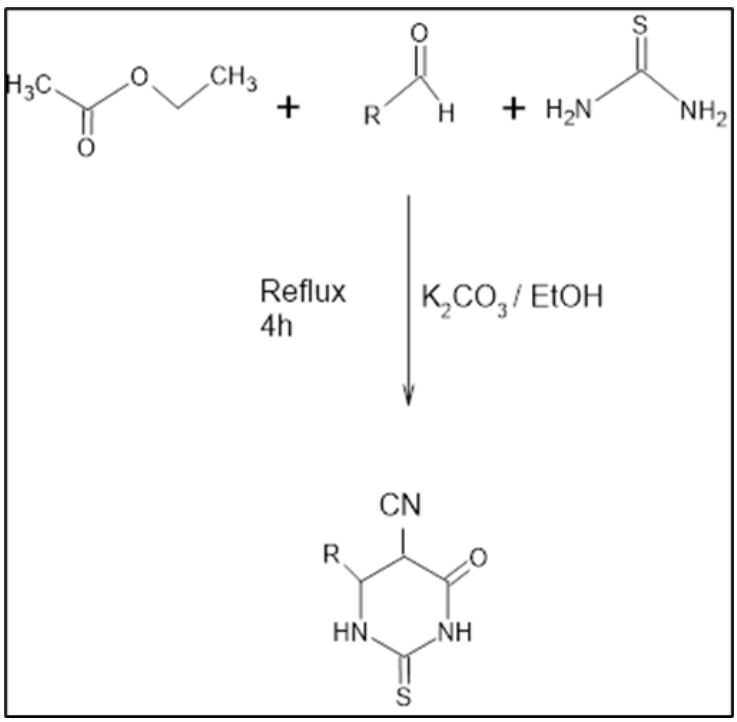
Figure 2 Alloxan (5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione)

2. Chemical synthesis of Pyrimidine Derivatives

Pharmaceuticals, useful materials, and natural items all include the pyrimidine substructure [7].Most synthetic pathways leading to this family of azaheterocycles rely on carbonyl compound and amine condensation [8,9]. Utilizing current developments in cross-coupling chemistry to add substituents to activated heterocycles is a complementing strategy to substituted derivatives [10].

2.1. From ethyl cyanoacetate

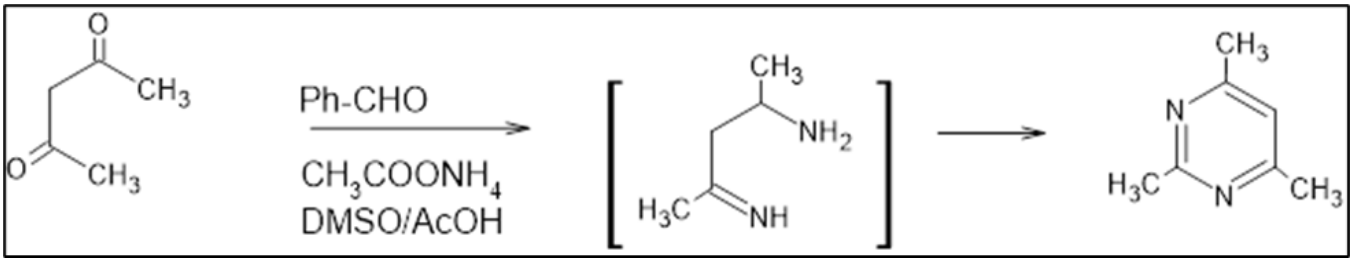
Through the use of potassium carbonate as a catalyst in conjunction with a combination of ethyl cyanoacetate (1), aldehyes (2), and thiourea (3), Kambe et al. produced 5-cyano-4-oxo-6-alkyl(aryl)-2-thioxo-1,2,3,4-tetra hydropyrimidine derivatives (4a-d) [11].



Scheme 1 Synthesis of pyrimidine derivatives from ethylcyano acetate

2.2. From acetyl acetone.

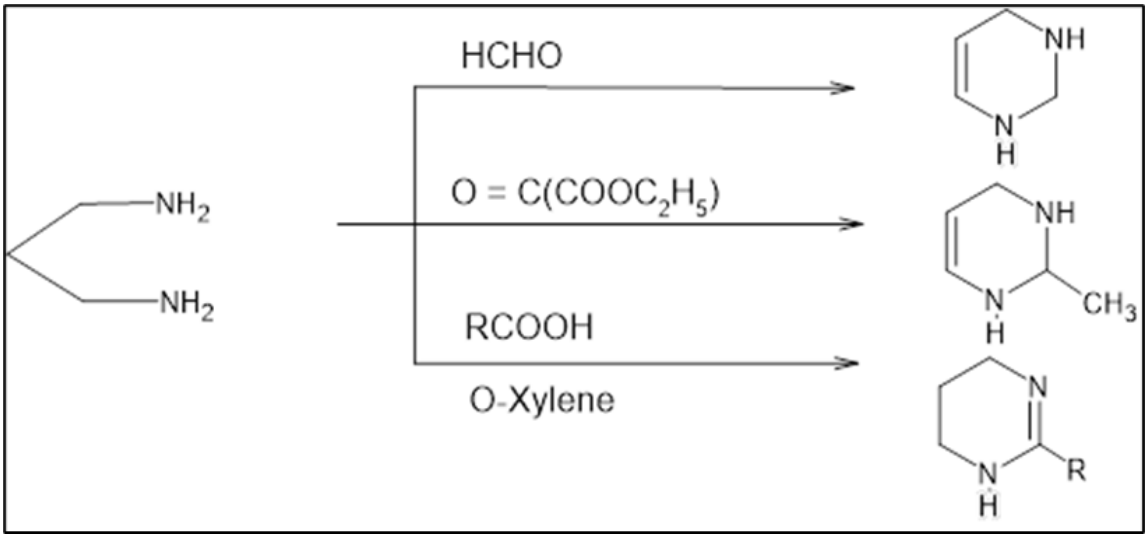
Lweis et al. created the pyrimidine derivatives (7) by reacting benzaldehyde and acetyl acetone (5) in the presence of two equivalents of ammonium acetate, which produced the intermediate (Z)-4-iminopent-2-en-2-amine (6). From there, a process produced the primidine derivative (7) (Scheme 2) [12].



Scheme 2 Synthesis of pyrimidine derivatives from acetyl acetone

2.3. From 1,3-diaminopropane.

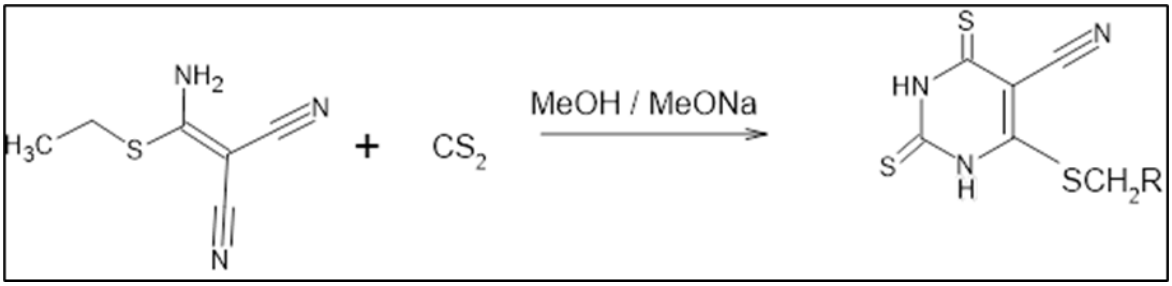
Fischer et al. disclosed on one of the most significant processes for creating tetrahydro pyrimidine derivatives from 1,3-diaminopropane. Developed by Grath et al., the process involved reacting 1,3-diaminopropane (8) with formaldehyde, diethyl carbonate, and carboxylic acid to produce the corresponding pyrimidine derivatives (9a-c) (Scheme 3). [13–14]



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

2.4. From Enaminonitrile.

Briel et al.'s work on the synthesis of heterosystems with pyrimidine moiety is still one of the most effective techniques. By using CS2 on enaminonitrile (10) in the presence of sodium methoxide, they were able to produce pyrimidinethione derivative (11) (Scheme 4) [15].



Scheme 4 Synthesis of pyrimidine derivative from enaminonitrile

3. Biological significance

Pyrimidine derivatives are a fascinating and varied class of pharmaceuticals that are crucial to biological processes. Medicinal chemists have created and employed a variety of pyrimidine scaffolds to create new therapeutics with a wide range of pharmacological activities, such as antitubercular, antibacterial, antifungal, anticancer, and anti- effects. Furthermore, thiamine, riboflavin, barbitone, and folic acid are among the vitamins that contain the pyrimidine ring (Fig. 3) [16].

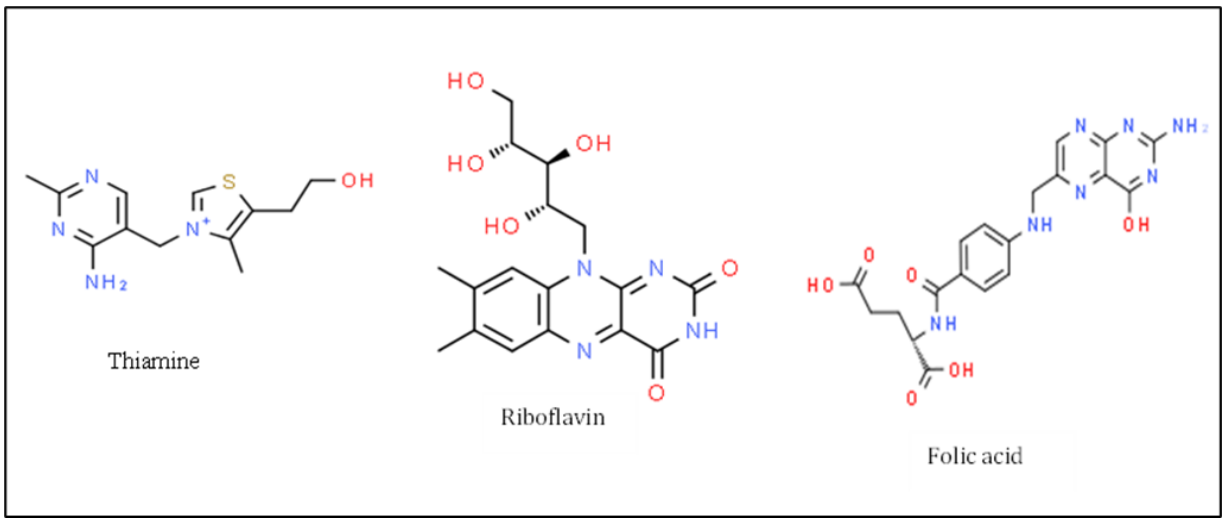


Figure 3 Structure of compounds containing pyrimidine

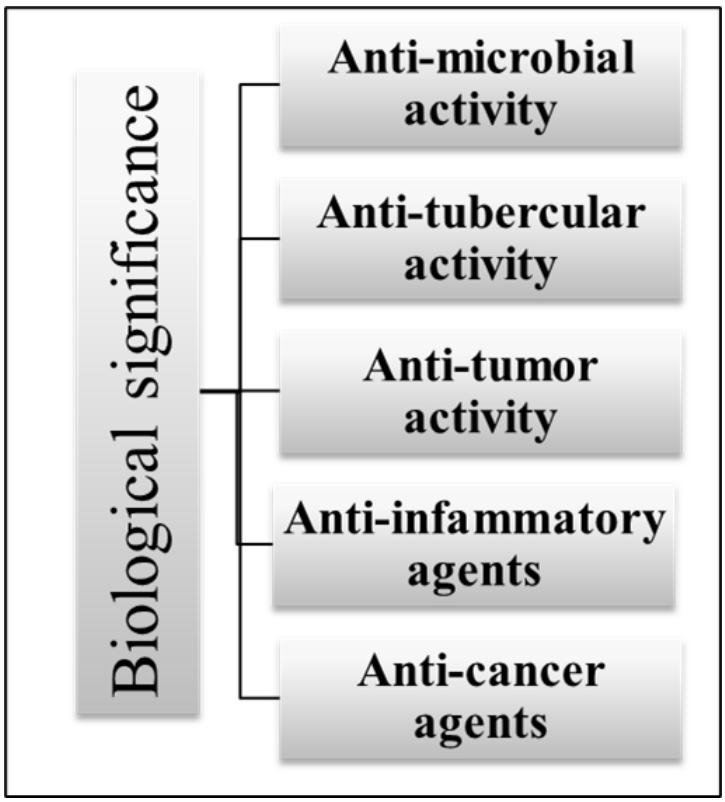


Figure 4 Biological significance of pyrimidine derivatives

3.1. Pyrimidine as an Anticancer Agent

One of the most dangerous diseases in the world today is cancer. To fully eradicate the disease, more powerful and efficient anticancer drugs still need to be developed, notwithstanding recent developments in the basic mechanisms underlying cancer [17].

According to reports, anticancer medications can cause resistance through a variety of methods. Efforts have been undertaken to minimize medication resistance in cancer. Against two hepatocellular carcinoma cell lines (HepG2 and Huh-7), as well as normal fibroblast cells, Ahmed et al. demonstrated the production and anticancer activity of pyrimidine pyrazoline-anthracene derivatives. When tested on the two cell lines, the proposed compounds demonstrated broad-spectrum anticancer action; moreover, their activity was more pronounced on cancer cells than on counter cells [18]. Comparing the anticancer activity of doxorubicin (DOX) against HepG2 and Huh7 cell lines, only compound (1 a-d) shown very good results. These compounds were shown to be the most promising anticancer agents against HepG2 and Huh-7 cells, as revealed by their structure activity relationship (SAR) investigations. These compounds triggered apoptosis in these cell lines by significantly activating caspase 3/7 at varying doses. After synthesizing new series 1H-pyrazolo[3,4-d]pyrimidine derivatives (Fig. 4), Gabera et al. assessed compound (2)'s antiproliferative properties against three cancer cell lines with EGFRWT (MCF-7, HepG2, A549) and two cancer cell lines with EGFRT790M (H1975 and HCC827). The compounds were also tested for their inhibitory activities against the epidermal growth factor receptor (EGFR) in the context of treating malignancy. According to findings from studies of cell cycle progression, this substance is an effective apoptotic agent that stops the G0/G1 and G2/M phases of the cell cycle [19].

El-Metwally and associates created an innovative range of thieno[2,3-d] pyrimidine derivatives in 2020 (Fig. 8), exhibiting an IC50 of approximately 4–10 μM against malignant HepG2 and MCF7 cells. Compound (Fig. 8) was the only one in their investigation to upregulate p53 expression by approximately 3-5 times and decrease Topo II expression by around 60%. Additionally, 40 demonstrated apoptotic induction, cell cycle arrest, and selective cytotoxicity [20]. The design, synthesis, and biological assessment of novel pyrimidine derivatives as anticancer drugs were the subjects of recent work by Madia et al. According to their findings, RDS 344, a newly synthesized aminopyrimidine molecule, may have anticancer properties. This substance prevents the growth of cells in glioblastoma, triple-negative breast cancer, oral squamous cell carcinomas, and colon cancer, among other malignancies. The benzyl substituent in RDS 3442, out of all the produced compounds, reduces the cell survival of tumor cell lines [21] In the meantime, Kuriwaki et al. conducted an anticancer study by thinking that bladder cancer patients would find fibroblast growth factor receptor 3 (FGFR3) to be an appealing therapeutic target. One of the pyrimidine derivatives that they have discovered causes tumor regression in a model of xenograft mice. Their research indicates that FGFR3 inhibitory activity is enhanced by inserting two fluorine atoms into the 3,5-dimethoxyphenyl ring, decreasing the molecular size of the substituent at the C4-position, and substituting the linker of the C5-position in the pyrimidine scaffold [22]. Furthermore, by focusing on various pathways that are accountable for the development of cancer, these pyrimidine analogs must screen for anticancer activity [23].

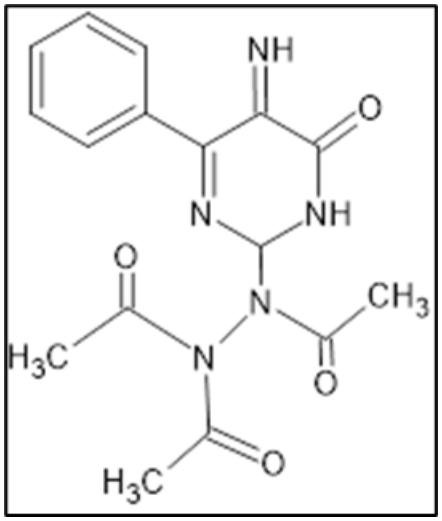


Figure 5 Anticancer Agent

3.2. Antimicrobial activity

Concerns have been raised about antibiotic resistance. Novel chemical scaffolds with potential antibacterial and antifungal properties are therefore desperately needed to stop the emergence of antibiotic resistance. The synthesis of pyrimidine analogs as antibacterial agents has been undertaken in an attempt to combat antibiotic resistance.

Researchers created novel sulfanilamide-pyrimidine compounds in 2020 by combining three-component sulfanilamide hybrids with azole rings or their analogs and pyrimidine. With equipotent or better activity compared to the existing therapeutic medicines, fluconazole and norfloxacin, new sulfanilamide derivatives effectively suppressed the growth of the tested strains. In addition to its effective membrane permeability, the derivative's strong activity against the tested microbes resulted from its capacity to intercalate into the bacteria' DNA to create a supramolecular complex [24] Fan et al. also reported synthesizing a variety of phenylthiazole and phenylthiophene pyrimidine diamines, citing structural similarities with a powerful compound (N2-isobutyl-N4-((4-methyl-2-phenylthiazol-5-yl)methyl) pyrimidine-2,4-diamine) as an example. Only N4-[5-(3-bromophenyl)thiophene-2-yl]methyl)-N2-isobutylpyrimidine-2,4-diamine has demonstrated the strongest antibacterial properties from the produced compounds, according to their research [25].

We developed a novel series of thieno[2,3-d]pyrimidines with hybrid bioactive moieties. Compound (4) (Fig. 9) in this collection had the strongest antibacterial activity against all tested bacterial strains. Comparing compound (5) to the standard, which has an inhibitory zone of 26 mm, the compound containing compound (5) had the maximum effective value against Candida albicans [26]. Using the agar diffusion technique, G. Shaaban et al. synthesized a series of new 3,4-dihydrothieno [2,3-d] pyrimidine derivatives and assessed their efficacy against six bacterial and three fungal species. The molecule had considerable antifungal activity and half the potency of levofloxacin as a positive control against P. aeruginosa, according to the data [27].

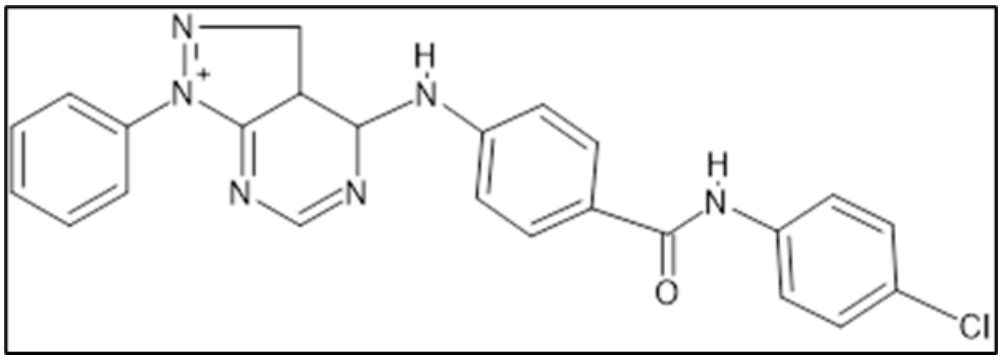


Figure 6 Antimicrobial agents

3.3. Antitubercular Activities

Numerous heterocyclics with anti-tuberculosis activity that are obtained from synthetic and natural sources have been reported. Nearly all of them have acquired drug resistance, necessitating the development of new anti-tubercular medications.

A novel scaffold for the treatment of tuberculosis was recently disclosed by Van der Westhuyzen et al. Based on their analysis, it appears that pyrimidinyl residue assimilation may have antitubercular efficacy. 28]. Additionally, as an anti-tubercular prodrug, 2-[4-mercapto-6-(methylamino)-2-phenylpyrimidin-5-yl]-ethan-1-ol (6) was synthesized, according to Chiarelli et al. [29]. Novel 32 ceritinib analogs were synthesized, and their anti-mycobacterial properties were reported by Liu et al. Only compound 5-Chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl) phenyl)-N4-(naphthalen-1-yl) pyrimidine-2,4-diamine (7) demonstrated notable antimycobacterial activity among these derivatives [30]. According to Modi et al.'s study, molecular docking investigations were used to construct 26 unique pyrazolo[1,5-a] pyrimidine analogs. Most of the compounds showed encouraging anti-tubercular action throughout their production [31]

3.4. Anti-Inflammatory Agents

"Anti-inflammatory" describes a substance's ability to lessen inflammation. Cell damage in illness conditions, especially autoimmune disorders, is mostly caused by inflammation. The hunt for innovative anti-inflammatory medications is of great importance in medical pharmacology due to the extensive influence of inflammatory processes in health problems.

Novel compounds to address inflammatory illnesses are also increasingly needed due to the discovery of new immune pharmacological targets.

Pyrimidine analogs have a history of being anti-inflammatory, according to published research. For this reason, Somakala et al. synthesized a large number of pyrimidine analogs in 2019 and evaluated them for BSA antidenaturation action, antioxidant test, and p38α MAP kinase inhibition in vitro (Fig. 10). They discovered that the substituted phenyl groups at the amide linkage of the pyrazolo-pyrimidine moiety enhanced the anti-inflammatory effect in vitro when compared to aliphatic derivatives. It was also found that the compounds have a robust anti-inflammatory impact and a low risk for ulcer formation [32]. Additionally, Vidal et al. have looked at the effects of hexahydroimidazo[1,2-c]pyrimidines on leukocyte activity in vitro in models of inflammation. According to their research, several of these substances inhibit the function of leucocytes, and HIP4, one of the potent derivatives, showed potent anti-inflammatory characteristics [33].

Abdelgawad et al. developed compounds with potent anti-inflammatory properties. It was shown that these candidates selectively inhibited COX-2 rather than COX-1. According to research on ulcerogenic liability, every examined chemical was comparable to celecoxib in terms of ulcerogenicity and less so than indomethacin. Selective COX-2 inhibitors appear to be made possible by the hybrid structure that combines the pyridine moiety with the pyrimidine scaffold [34]. Synthesized compounds with anti-inflammatory and EGFR-TK (epidermal growth factor receptor tyrosine kinase) inhibitory effects were produced using the fragment-based drug design approach. According to SAR analysis, anti-inflammatory action is reduced when the electron-donating group is substituted for the standard [35]. Synthesis was done on a number of fused thiophene, coumarin, pyrrole, arylhydrazon, and 4-methoxyphenyl butenyl derivatives with pyrimidine rings. The compound's coumarin moiety was shown to have distinct anti-inflammatory capabilities by the anti-inflammatory activity screening [36].

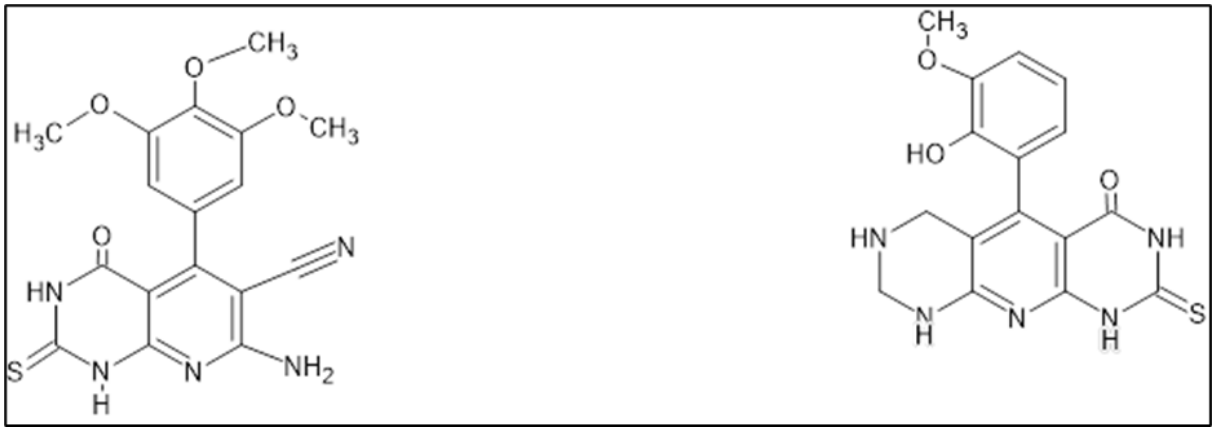


Figure 7 Anti-inflammatory agents

3.5. Antitumor activity

The creation of cancer drugs is crucial to medicinal chemistry. Recent reports have indicated that pyrimidine derivatives exhibit significant anticancer activity. Numerous antimetabolites based on pyrimidines were created because they shared structural similarities with the body's own substrates. The dependent sugar groups and/or the pyrimidine ring are two examples of these structural alterations [37]. Early metabolites that were generated included 5-fluorouracil (5-FU) and its derivatives. Interfering with mRNA translation and DNA synthesis is the primary mode of action. However, because of its nonspecific cytotoxicity, this type of derivative exhibits a number of adverse effects. To get over these drawbacks, the 5-FU structure underwent a few modifications. The pyrimidine ring's carbon 5 locations are where fluorine is used in place of hydrogen for the management of numerous solid malignant tumors [38].

The production and anticancer efficacy of new pyrimidine derivatives against the cell lines (DU-145) were reported by Sridhar et al. According to this study, the pyrimidine nucleus's 4-chlorophenyl substitution enhanced its anti-cancer effectiveness [39]. The synthesis of piperidinyl-substituted [1,2,4]triazolo[1,5-a] pyrimidines was reported by the Sánchez-Moreno group in 2020. The majority of the compounds exhibited moderate anti-HIV effectiveness and low cytotoxicity (CC50> 200 μM). According to Shanmugasundaram, P., and colleagues, pyrido[2,3-d] pyrimidine carboxylate was synthesized. by three human cancer cell lines—colon (HT29), liver (HepG2), and cervical (Hela cell)—the anticancer properties of synthetic pyrimidine derivatives were assessed by the MTT survey and were found to be significantly active. For each of these cell lines, the lethal dose (LC50) of the produced pyrimidine derivatives was

determined to be greater than 100 μg/ml [40]. Recently, pyrimidine analogs were designed via pharmacophore-fusing design to find powerful non-nucleoside HIV-1 reverse transcriptase inhibitors. We developed and produced two series of cyanovinyl- and biphenyl-pyrimidine sulfonylacetanilide. In HIV-1-infected MT-4 cells, these substances showed nanomolar action against the WT virus and several drug-resistant mutant strains. Using non-nucleoside reverse transcriptase inhibitors, compound, which is thought to be the most effective in this series, was subjected to a docking analysis that revealed two hydrogen bonds between residues Y188 and K223 and compound 56. Additionally, the hydrophobic sites (Y181, Y188, F227, and W229) and the Pro236 loop were well-fitted by the biphenyl fragment, and the sulfonylacetanilide moiety was visible [41].

4. Recent Development in Pyrimidine-Based Drug Development

Cancer is a worldwide health concern that lowers life expectancy and has a number of negative side effects from therapy. Finding new anticancer medications has become necessary as a result of cancer cells' resistance to current treatments. A special structure found in living things, pyrimidine is essential to many biological processes, including the etiology of cancer. Owing to structural similarities with the nucleotide base pair of DNA and RNA, it is acknowledged as a beneficial molecule for cancer treatment [42].

An entirely new class of pyrimidine-5-carbonitrile compounds has been developed as ATP-mimicking EGFR tyrosine kinase inhibitors. A panel of four human tumor cell lines, including colorectal carcinoma (HCT-116), hepatocellular carcinoma (HepG-2), breast cancer (MCF-7), and non-small cell lung cancer cells (A549), were used to test the in vitro cytotoxic effects of these drugs. It was discovered that five of the synthesized compounds—11a, 11b, 12b, 15b, and 16a—had more potent antiproliferative activity than the EGFR inhibitor erlotinib when tested against the evaluated cell lines. Compound 11b, in instance, demonstrated erlotinib activity against HCT-116, HepG-2, MCF-7, and A549 cells at 4.5–8.4 times the concentration, with IC50 values of 3.37, 3.04, 4.14, and 2.4 μM, significantly.

Additionally, utilizing the homogeneous time resolved fluorescence (HTRF) test, the most cytotoxic compounds that shown promising IC50 values against the four cancer cell lines were investigated further for their kinase inhibitory effects against EGFRWT and EGFRT790M. Moreover, compound 11b was discovered to be the most effective against the mutant EGFRT790M and EGFRWT, with IC50 values of 4.03 μM and 0.09, respectively. Compound 11b can cause a strong apoptotic effect in HCT-116, HepG-2, and MCF-7 cells as well as arrest the cell cycle at the G2/M phase, according to assessments of the cell cycle and apoptosis. Furthermore, in HepG-2, compound 11b increased caspase-3 levels by 6.5 times relative to the control.

Lastly, molecular docking analyses were performed to investigate the synthesised drugs' binding mode against the suggested targets, EGFRWT and EGFRT790M. To investigate drug-likeness qualities, more in silico ADMET investigations were carried out [43].

Following the entry of three medications—GSK 2556286 (GSK-286), TBA7371, and SPR720—into clinical trials, interest in small compounds with antitubercular action and the pyrimidine motif in their structures has increased. In an effort to emphasize the structural diversity of antitubercular pyrimidine-containing compounds, this study summarizes current developments in hit-to-lead drug discovery investigations. The review addresses pyrimidine compounds based on their intended uses in the first section, outlining the structure-activity connections within each pyrimidine family. This review's second section, which categorizes the compounds based on their structural characteristics, focuses on antitubercular pyrimidine derivatives that have an unidentified or speculative target [44].

Some artificial nitrogen-based heterocyclic compounds, such PJ34, have demonstrated strong anticancer activity recently. As a result, we created and synthesized novel compounds that had a nitrogen-containing scaffold and assessed how well they inhibited tumor cell proliferation. The effects of three recently created substances on cell lines from three distinct human cancers—triple-negative breast cancer, colon carcinoma, and glioblastoma—are described here. It was discovered that while the third of these chemicals considerably reduced the three cell lines' ability to replicate, the other two had no effect on proliferation. Furthermore, when this third molecule was utilized at greater concentrations (30–50 μM), it produced apoptosis in all three cell lines and caused the overexpression of p21 and p27 as well as the blocking of the cell cycle at G0/G1. The findings show that this substance is a strong apoptosis inducer, replication inhibitor, and negative regulator of cell cycle progression for cancer cells of various histotypes. Our findings point to this novel molecule's potential use as an intriguing and potent tool for novel therapeutic strategies against a range of malignancies [45].

In the twenty-first century, bacterial infections resistant to many drugs have emerged as a significant cause of clinical death. To overcome this obstacle, a lot of work has been done. Bacterial resistance is being addressed in part by the

sensible use of antibacterial medications with various structural kinds and mechanisms in combination with the discovery of new antimicrobial agents. Currently, the main focus of novel antibacterial medication discovery is on drugs that include pyrimidines. Many scientists are now interested in pyrimidine-containing heterocyclic compounds due to their favorable activities and variety of modes of action. Furthermore, pyrimidine derivatives can interact with genetic materials, enzymes, and other biopolymer substances in the cell since pyrimidine structure is a crucial component of many endogenous chemicals. Researchers have concentrated on finding and refining the structures of pyrimidine derivatives, leading to the identification of numerous unique compounds with fascinating characteristics. We compiled the therapeutic potentials of pyrimidine compounds that show promise for antibacterial applications over the past 10 years in this mini-review. Specifically, a thorough discussion was held regarding the connections between the structures of modified pyrimidines and their antibacterial activity [46].

4.1. Marketed Drugs Containing Pyrimidine

Many pyrimidine derivatives have found extensive clinical applications during the past three decades after being developed as therapeutic agents. Pharmacological uses for them include antineoplastic, antiviral, and antibacterial treatments; they are also used as an expectorant, anti-parkinsonian, anthelmintic, vasodilator, liver disease, drugs for peripheral neuropathies, and drugs for hyperuricemia-related disorders [47]. The pyrimidine ring possesses distinct physiochemical properties that have made it a popular scaffold for a wide range of biological targets with varying therapeutic requirements. The chemical space portfolio of drugs relying on this privileged scaffold has grown at a rapid pace. (Table 1) lists more pharmacological properties and clinical implications of marketed drugs. Additionally, by serving as bioisosteres for phenyl and other aromatic π systems, they frequently improve the pharmacokinetic/pharmacodynamic properties of the drug.

Table 1 Marketed Drugs made with Pyrimidine Derivatives

S/N0	DRUG	MOLECULAR FORMULAR	DRUG CATEGORY	STATUS	Ref.
1	Osimertinib	$C_{28}H_{33}N_7O_2$	Anti-cancer	Approved	[48]
2	Estravirine	$C_{20}H_{15}BrN_6O$	Anti-viral	Approved	[49]
3	Tegafur	$C_8H_9FN_2O_3$	Antimetabolite	Not FDA-approved but used in combination with uracil in many countries	[50]
4	Rilpivirine	$C_{22}H1_8N_6$	Antiviral	Approved	[51]
5	Trimethoprim	$C_{14}H_{18}N_4O_3$	Antibacterial	Approved	[52]
6	Flucytosine	$C_4H_4FN_3O$	Antifungal	FDA approved	[53]
7	Iclaprim	$C_{19}H_{22}N_4O_3$	Antibiotic	Approved	[50]
8	Cyprodinil	$C_{14}H_{15}N_4$	Antifungal	Approved	[50]
9	Pralsetinib	$C_{27}H_{32}EN_9O_2$	Anticancer	Approved	[50]
10	Nilotinib	$C_{28}H_{22}F_3N_7O$	Anticancer	Approved	[50]
11	Imatinib	$C_{29}H_{31}N_7O$	Antitumor	Approved	[50]
12	Piromidic Acid	$HIO_4H_5IO_6$	Quinolone antibiotic	Not FDA- approved	[54]
13	Brodimoprim	$C_{13}H1_5BrN_4O_2$	Anti-bacterial	Not FDA- approved	[55]
14	Eprizole	$C_{17}H_{11}N_5O_4S$	Anti-inflammatory	Approved	[50]
15	Glipizide	$C_{21}H_{27}N_5O_4S$	Anti-diabetic	Approved	[50]
16	Neohetramine	$C_{16}H_{22}N_4O$	Antihistamine	Approved	[50]
17	Morantel Citrate	$C_{18}H_{24}N_2O_7S$	Antibiotics	Not FDA-approved	[56]

18	Buspirone	$C_8H_9FN_2O_3$	Antipsycotic	Approved	[50]

It makes sense that pyrimidine is a component of a large number of commercially available medications that are used to treat a wide range of illnesses, both infectious and non-infectious. These medications include antibiotics, antitumor, antiviral, anticancer, and anti-inflammatory medications.

5. Impact of Pyrimidine Derivatives in Diseases Treatment

5.1. Role of Pyrimidine Derivatives in Cancer Treatment

Newly created Pyrido[2,1-b] quinazoline fused compounds with promising therapeutic characteristics were disclosed by Bathula et al. (2019). Through in vitro studies against a variety of malignant cell lines, such as NCI-H460, A549, HCT-15, HT-29, HFL, and DU-145, these designed compounds were evaluated for their cytotoxic properties. Specifically, 1-(1-benzyl-1H-indol-3- y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline demonstrated the highest level of cytotoxic action against the lung cancer cell lines, A549 and NCI-H460. Furthermore, it was shown that the same substance had a strong anticlonogenic effect on lung cancer cells. This special chemical was shown to disrupt the G0/G1 cell cycle phase in the carcinogenic A549 cell lines using flow cytometry. In order to forecast the compounds' binding to the EGFR kinase, molecular docking experiments of the compounds were also carried out using erlotinib as the control. Comparing the drugs under investigation to erlotinib, similar interactions were observed. According to the study's findings, 11-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline has the potential to be a potent anticancer drug [57]. Likewise, Jian et al. stated in 2020 that they had synthesized 26 novel pyrazolo[3,4-b]pyridine-bridged derivatives of combretastatin A-4, obtaining 3,4,5-trimethoxylphenyl groups, and evaluated their anti-proliferative and tubulin polymerization-inhibiting properties. The preliminary biological evaluation determined that a small number of the potential compounds exhibited significant anti-proliferative activity against four different cell lines, namely MDA-MB-231, MCF-7, Kyse150, and HeLa. turned out to be the extremely effective pyridine derivative, causing HeLa cells to arrest in the G2/M stage in a dose-dependent manner. According to a molecular modeling study, analogue 1 appears to reside in tubulin's colchicine site. The initial results suggest that 3,4,5-trimethylphenyl modified pyrazolo[3,4-b]pyridine is a capable scaffold for the development of potent tubulin barriers as anti-tumor drugs [58].

Zwergel et al. (2021) created four aza-analogues, which are similar to the regioisomers from N-hydroxy-3-(4-(2-phenylbutanoyl)amino)phenyl)acrylamide. The pyridine nucleus in this acrylamide is what the same group previously found to be an HDAC inhibitor. When N-hydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylamide was first screened against mHDAC1, it was found to be a highly efficient inhibitor. Therefore, the same group of researchers generated both pyridylacrylic and nicotinic-based hydroxamates (11 compounds) and 20-aminoanilides (12 compounds) linked to N-hydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylamide, which needed to be tested against HDACs. All things considered, a single nicotinic hydroxamate showed sub-nanomolar efficacy and selectivity up to 34,000 times relative to HDAC4 and 100–1300 times relative to all other HDAC isoforms. When tested with U937 leukemia cells, three additional hydroxamates—1, 2, and 3—inhibited over 80% of cells in the G2/M stage of the cell cycle; however, the anilides had no effect on the progression of the cell cycle. In the same cell line, anilide 2 showed 40% cytodifferentiation, while hydroxamate 2 and anilide 1 both accelerated about 30% apoptosis.

Finally, Nhydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylamide, hydroxamate 2, anilide 1, 2 and 3 (Fig. S5), which were extremely effective analogues in leukemia cells, were also tested against K562, HCT116, and A549 cancer cells, demonstrating anti-proliferative properties [59].

The biological evaluation and computational quantum compound analysis of a newly synthesized heterocyclic sulfur thiophene analogue, comprising pyridine and 1,2,3-triazole components, namely BTPT [2-(1-benzyl-5-methyl-1H-1,2,3-tria zol-4-yl)-6-methoxy-4-(thiophen-2-yl) pyridine], were presented by Murugavel et al. (2019). BTPT drug similarity characteristics were searched using in silico medic's examination of internal ADMET qualities. For molecular docking investigations, human topoisomerase IIa targeting the ATP binding site was utilized. The three human malignant cell lines PC-3, A549, and MDAMB-231 were subjected to the MTT assay as part of the BTPT/doxorubicin in vitro cytotoxicity test. By contrast with the well-known cancer medication doxorubicin, the lead chemical BTPT demonstrated significant cytotoxicity against MDAMB-231 (a breast cancer cell), moderate action with A-549 (a human lung cancer cell), and minimal inhibition with PC-3 (a human prostate cancer cell). It was suggested that BTPT would make a strong anticancer medication [60].

5.2. Pyrimidine-Based Drug for Treatment of Infection

5.2.1. Pyrimidine as antivirals

An intriguing study on pyrimidines as anti-infective drug scaffolds was developed by Kang et al. [61]. This work effectively explored acquired immunodeficiency syndrome (AIDS), which is caused by the human immunodeficiency virus (HIV). HIV was once considered a fatal illness, but with the development of antiretroviral medication, the diagnosis has been modified to one of manageable chronic illness. The authors concentrated on creating non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are frequently found in antiviral medications, in their endeavor. Mutant strains caused severe drug resistance to the first- and second-generation NNRTIs that were administered, making these medications useless. While E138K developed toward second-generation medications, the most prevalent mutant strains, K103N and Y181C, developed against first-generation treatments [62].

In addition, Liu et al. worked to create a novel medication that would inhibit HIV-1 reverse transcriptase (RT) in order to cure AIDS [63]. For the molecular functions of ribonuclease H and DNA/RNA-dependent DNA polymerase involved in viral replication, RT is crucial [64]. RT inhibitors are currently primarily classified as either non-nucleoside RT inhibitors (NNRTIs) or nucleoside RT inhibitors (NRTIs) [65]. Because of their excellent specificity, relatively low toxicity, and promising anti-HIV-1 effects, NNRTIs have been essential components of highly active antiretroviral treatments. The authors of this paper stress the need for novel non-retroviral therapeutics (NNRTIs) with enhanced pharmacological characteristics and increased anti-HIV-1 actions against resistant mutant strains.

In an effort to target the influenza virus, Chen et al. have worked to optimize a pyrimidine-based pharmacological scaffold [66]. Influenza is a respiratory tract infection that causes over 300,000 deaths annually globally and has a significant negative social and economic impact on society [67]. successful use of the influenza vaccination can reduce this burden, but it is not always successful because of antigenic drift and mismatches between circulating strains and the vaccine. Notwithstanding the fact that RNA polymerase (RNAP) inhibitors (Baloxavir, see Supplementary Materials) and neuraminidase inhibitors (Oseltamivir, see Supplementary Materials) are used as first-line-of-defense medications, drug-resistant mutations have developed, prompting efforts to create new direct-acting antivirals in order to counteract these mutations and find new medications with unique mechanisms of action [68]. In order to bind aza-β 3- or β 2,3-amino acids on a 7-azaindole ring to the RNAP component PB2, which has shown to be a prime target for antiviral medication development, these researchers proposed a medicinal chemistry technique. A pyrimidine was connected to aza-β-amino acid motifs of various sizes, shapes, steric hindrances, and configurations, which benefited from easy structural elaboration, and their antiviral properties were assessed.

5.2.2. Pyrimidine as antibacterials

The goal of Luo et al. [69] has been to create a lead molecule that can combat tuberculosis (TB), a deadly infectious illness that is primarily found in Asia and Europe and is caused by the mycobacterium tuberculosis [70]. Even though the combined regimen used in the present treatment procedure for this infection is very effective, resistance to these treatment choices has begun to appear. Therefore, to combat drug-resistant tuberculosis, a promising antitubercular molecule with a unique mode of action needs to be created. Through a phenotypic screening technique, the authors of this paper observed that Certinib, an approved anticancer medication for anaplastic lymphoma kinase, displayed antitubercular capabilities. When tested against the H3Ra virant, the chemical showed a moderate minimum inhibitory concentration (MIC) of 9.0μM/ml.

The Yang research group has been working to develop an antibiotic with a wider spectrum by adding a pyrimidine ring to the structure of Linezolid [71]. It is well known that oxazolidinone ring cores have strong antibacterial properties, particularly against Gram-positive infections [72]. To create next-generation antibiotics, however, ongoing advancements over existing drugs are required due to the infections' widespread resistance. The authors primarily targeted urinary tract infections when searching for antibiotic options that would also have antibiofilm efficacy. The scientists postulated that adding a pyrimidine moiety to the Linezolid structure would increase the compound's permeability and enhance the drug's capacity to generate hydrogen bonds.

5.2.3. Pyrimidine as antifungal

In order to combat a number of fungal infections, such as candida albicans, Saccharomyces cerevisiae, and candida parapsilosis, a novel class of safe and non-toxic anti-infective agents was developed in a patent by Li et al. [72]. Using K2CO3 in acetine to react with ethyl chloroformate to produce aryl fomylurethanes, the potent describes the manufacture and assessment of several pyrimidine derivatives from aryl sulfonamides. Subsequent reactions with different substituted 2-amino pyrimidines led to the production of sulfonyl ureas.

6. Conclusion and future prospective

The various uses of pyrimidine derivatives in drug research and treatment are highlighted by this study. As this review has shown, it is clear that pyrimidine derivatives have been studied for various illnesses. Despite the fact that pyrimidine and its derivatives are said to have a variety of pharmacological actions and functions, including those of antibacterial, anticancer, anti-inflammatory, and antitubarcular agents. This chemical is highly beneficial to the pharmaceutical sector. However, there are a number of obstacles in the way of creating novel pyrimidine derivatives, such as the requirement for increased pharmacokinetic property understanding, decreased toxicity, and improved selectivity. All things considered, the current research in this area is promising for the development of fresh, efficient therapies for a variety of illnesses. Further research in this area is still possible in the hopes of discovering a breakthrough pharmacological action. Additionally, new research on pyrimidine derivatives is desperately needed because existing medications are no longer effective.

Compliance with ethical standards

Disclosure of conflict of interest

All the authors have decleared no any conflict of interest.

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