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A detailed review of recent developments in the synthesis of pyrimidine derivatives and their anticancer potential.

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Abstract

Pyrimidine derivatives are important in anticancer drug discovery because they mimic nucleic acids and can create hydrogen bonds and π-π interactions. This review explores various synthetic approaches, including traditional Biginelli and β-dicarbonyl condensations, as well as multicomponent, green, microwave-assisted, and catalyst-driven methods that improve efficiency and sustainability. We examine the structure-activity connections behind antimetabolite, kinase inhibitor, and DNA intercalator actions, including clinically authorized medicines such as 5-fluorouracil, capecitabine, gemcitabine, and pemetrexed. Recent breakthroughs in hybrid scaffolds, epigenetic modulators, and AI-driven design are reviewed, as well as the difficulties of resistance, toxicity, and scalability. Future directions include sustainable synthesis, machine learning optimization, and targeted degradation techniques.

Keywords: Pyrimidine, Cancer, FDA, Synthesis, SAR.

1. Introduction

Cancer remains one of the top causes of death globally, necessitating the ongoing development of effective and targeted chemotherapeutic treatments.[1] Heterocyclic compounds, particularly those containing nitrogen atoms, have received a lot of interest because of their broad pharmacological spectrum.[2] Among these, pyrimidine and its derivatives stand out as important scaffolds in anticancer drug discovery.[3] Pyrimidines are naturally occurring nucleic acid components, specifically cytosine, thymine, and uracil, highlighting their biological significance and compatibility with cellular machinery.[4]

Historically, pyrimidine compounds have demonstrated a wide range of pharmacological effects, including antiviral, antibacterial, anti-inflammatory, and, most importantly, anticancer activity.[5] Several FDA-approved anticancer medicines, including 5-fluorouracil and capecitabine, contain pyrimidine nuclei, emphasizing the importance of this scaffold in drug design. Novel pyrimidine-based compounds with increased selectivity, potency, and lower toxicity have been developed thanks to advances in synthetic chemistry. [6]

This review intends to provide an in-depth summary of the synthetic techniques used for pyrimidine derivatives and to examine their anticancer potential using recent literature. It is an invaluable resource for medicinal chemists and researchers working on the design and development of novel anticancer medicines.

2. Chemical Structure and Biological Importance of Pyrimidine

Pyrimidine is a six-membered aromatic heterocycle that contains two nitrogen atoms at positions one and three. Its planar form and electron-rich nitrogen atoms enable hydrogen bonding and π-π interactions, which are necessary for interacting with biological targets like enzymes and nucleic acids.[7] The fundamental pyrimidine ring serves as the foundation for a wide range of naturally occurring and synthesized compounds with significant pharmacological effects. Pyrimidines are essential components of nucleic acids. Cytosine, thymine, and uracil are pyrimidine bases found in DNA and RNA that play critical roles in genetic coding, replication, and cell function. Synthetic pyrimidine derivatives are similar to natural bases, allowing them to interact well with nucleic acid-related enzymes, hence inhibiting DNA/RNA production in cancer cells.[8,9] This explains their widespread use in anticancer therapy. Substituted pyrimidines have a variety of biological actions depending on the nature and position of their substituents. For example, the addition of electron-withdrawing groups or electron-donating groups can have a considerable impact on lipophilicity, bioavailability, and target binding. Furthermore, fused pyrimidines have been demonstrated to have higher cytotoxic effects due to increased structural stiffness and better interaction with DNA or enzymes.[10] The versatility of the pyrimidine scaffold in rational drug design is further demonstrated by its inclusion in kinase inhibitors, antimetabolites, and DNA-intercalating agents. These derivatives act through diverse mechanisms, including inhibition of dihydrofolate reductase, thymidylate synthase, and various tyrosine kinases involved in cancer cell proliferation.[11] Consequently, pyrimidine serves as a privileged scaffold in medicinal chemistry, enabling the creation of structurally diverse and biologically potent anticancer agents.

3. Synthetic Strategies for Pyrimidine Derivatives

The synthesis of pyrimidine derivatives has been extensively explored due to their prominent role in pharmaceutical chemistry. A wide variety of synthetic strategies have been developed, ranging from classical condensation reactions to modern green and multicomponent approaches. The choice of synthetic route is often influenced by the desired substitution pattern and functional group compatibility.

3.1 Classical Synthesis Approaches

Traditionally, pyrimidines are synthesized via the Biginelli reaction or by the condensation of β-dicarbonyl compounds with amidines, urea, or guanidine. The most common classical method involves the cyclocondensation of 1,3-dicarbonyl compounds (like acetylacetone) with urea or thiourea in the presence of acid catalysts. These methods are robust and yield the desired pyrimidine rings under reflux conditions.

In 2015, Akhter et al. described a convenient one-pot, Biginelli-type cyclocondensation for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones, employing anhydrous $ZnCl_2$ as Lewis' acid catalyst under reflux in a heptane-toluene media.[12]

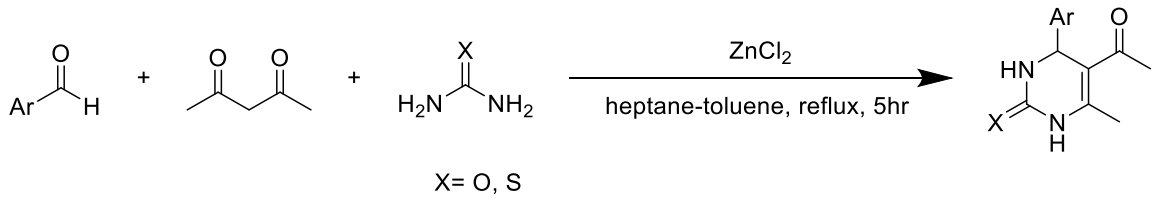

Figure 1: Reaction scheme by Akhter et al.

3.2 Multicomponent Reactions (MCRs)

MCRs are widely employed for the synthesis of structurally diverse pyrimidines. These reactions involve three or more components in a single-pot reaction, offering high atom economy and operational simplicity. One example includes the three-component reaction of aldehydes, β-keto esters, and urea, forming dihydropyrimidinones, which are key intermediates in the synthesis of bioactive molecules like monastrol. In 2014, Dharma Rao et al. developed a greener Biginelli-type multicomponent route. They used in situ transesterification of tert-butyl β-ketoester with various alcohols, followed by condensation with arylaldehyde and urea under solvent- and catalyst-free conditions at 110 °C for 3 hours. Following simple aqueous workup and ether washes, this one-step process produced 3,4-dihydropyrimidin-2(1H)-one C5-ester derivatives in isolated yields ranging from 85% to 94%.[13]

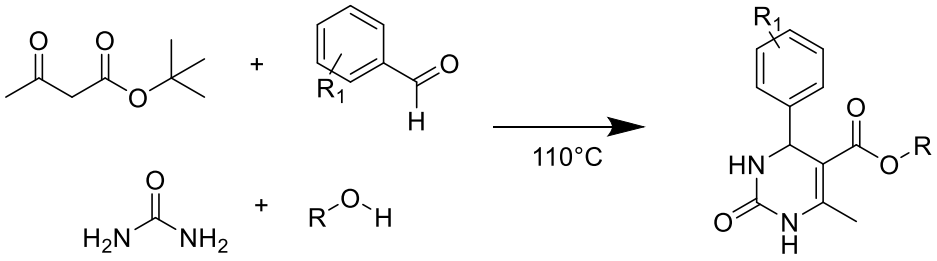

Figure 2: Reaction scheme by Dharma Rao et al.

3.3 Green and Microwave-Assisted Synthesis

In recent years, sustainable synthesis approaches have gained momentum. Microwave-assisted synthesis allows rapid heating and reduced reaction times, resulting in higher yields and cleaner reactions. Solvent-free and water-mediated conditions also align with green chemistry principles. Ionic liquids, solid acid catalysts, and biocatalysts have also been explored to improve the eco-friendliness of pyrimidine synthesis. In 2011, Raghuvanshi and Singh developed an efficient, solvent- and catalyst-free, microwave-assisted multicomponent protocol for 2,4-diamino-5-pyrimidinecarbonitriles . They condensed equimolar aromatic aldehydes, malononitrile, and guanidine in 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) under 100 W microwave irradiation at 60 °C for 2–3 min. This one-pot method afforded 2,4-diamino-5-pyrimidinecarbonitrile derivatives in 90–96 % yields, and the ionic liquid was recyclable for at least five cycles without loss of activity.[14]

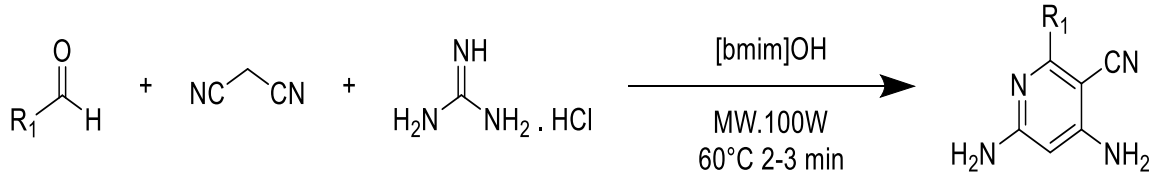

Figure 3: Reaction scheme by Raghuvanshi and Singh

Later, in 2018, Tiwari et al. reported a green, ionic-liquid–promoted synthesis of tetrahydropyrimidine-5-carboxylate and carbohydrazide hybrids. Using triethylammonium hydrogen sulfate ([Et_3NH][HSO_4]) as both solvent and Brønsted acid catalyst, they refluxed 4-oxo-4H-chromene-3-carbaldehydes, ethyl acetoacetate (or hydrazine hydrate), and urea (or hydrazide) at 100 °C for 60 min under solvent-free conditions. This method delivered six novel chromone–pyrimidine derivatives in 86–95% yields with simple aqueous workup and excellent catalyst recyclability, demonstrating a sustainable alternative to traditional Biginelli reactions.[15]

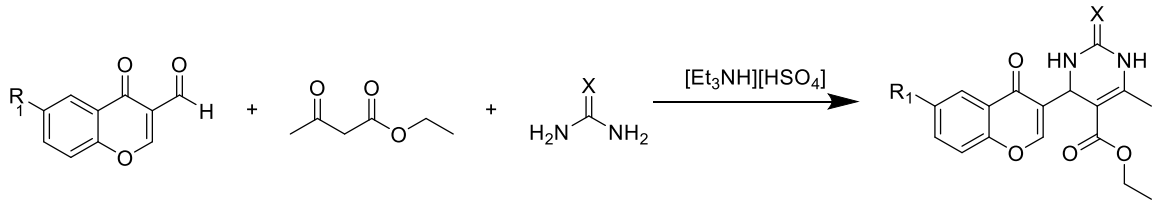

Figure 4: Reaction scheme by Tiwari et al.

3.4 Catalyst-Assisted Synthesis

Various catalysts such as Lewis acids (e.g., $ZnCl_2$, $AlCl_3$), organocatalysts, and nanocatalysts (e.g., TiO_2, Fe_3O_4 nanoparticles) have been utilized to enhance reaction rates and selectivity. Transition metal-catalyzed cross-coupling reactions have enabled the functionalization of pyrimidine rings at specific positions, enabling the development of highly substituted and functionalized analogs. In 2009, Sasada et al. reported a pioneering $ZnCl_2$-catalyzed, three-component coupling for the direct synthesis of 4,5-disubstituted pyrimidines. In their protocol, a functionalized enamine (1 equiv), triethyl orthoformate (3 equiv), and ammonium acetate (2 equiv) are stirred in toluene (PhMe) with 10 mol % $ZnCl_2$ at 100°C for 20 h. This single-step annulation proceeds via initial acetal activation by $ZnCl_2$, formation of a vinylamidine intermediate, and intramolecular cyclization to furnish the desired pyrimidine core in up to 99 % yield. The method tolerates a variety of enamines bearing electron-donating or -withdrawing aryl groups, as well as simple methyl ketones, producing mono- and disubstituted pyrimidines cleanly. $ZnCl_2$ loading, moderate temperature, and operational simplicity distinguish this approach from classical multi-step routes, offering a general, high-yielding, and scalable entry to substituted pyrimidines under relatively mild Lewis-acid catalysis.[16]

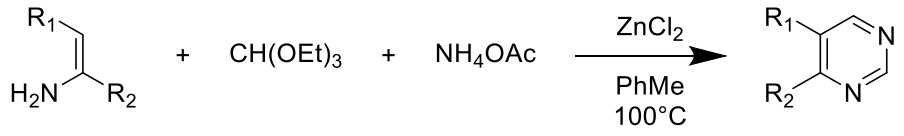

Figure 5: Reaction scheme by Sasada et al.

3.5 Recent Advances in Pyrimidine Synthesis

Recent advances have focused on regioselective synthesis, metal-free conditions, and flow chemistry techniques. Researchers have developed novel annulation strategies involving alkynes, nitriles, and diazonium salts for pyrimidine construction. Additionally, C–H activation strategies have enabled direct functionalization of pyrimidine cores, streamlining synthesis and expanding structural diversity.

In 2015, Guo et al. developed a metal-free, base-mediated C–H amination method to access polysubstituted pyrimidines under green conditions. Benzamidine hydrochloride and cinnamaldehyde (1.2:1 molar ratio) are stirred with KOH (2 equiv.) in DMSO at 120°C under O_2 for 12 h. This straightforward, one-pot protocol avoids transition metals and harsh oxidants, tolerates diverse substituents, and delivers 2,4-diaryl pyrimidines in up to 89 % yield, highlighting a sustainable advance in pyrimidine synthesis.[17]

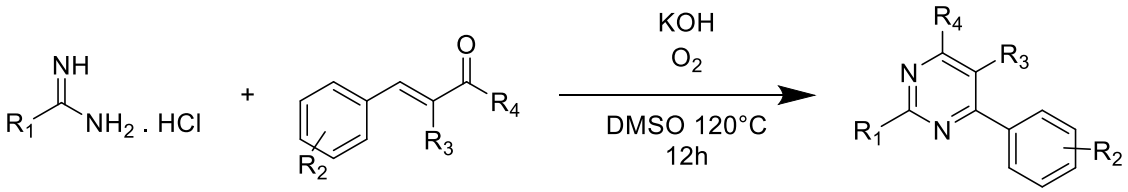

Figure 6: Reaction scheme by Guo et al.

4. Pyrimidine Derivatives with Anticancer Activity

Pyrimidine derivatives are a privileged scaffold in anticancer drug design, their two nitrogen atoms and planar ring enabling hydrogen-bonding and π–π interactions with diverse targets. Structural flexibility through substitutions at N^1/N^3, C-2/C-4, and C-5/C-6 allows precise tuning of pharmacokinetics and pharmacodynamics. Many analogues mimic natural nucleosides to inhibit DNA synthesis, while others act as ATP-competitive inhibitors of kinases such as EGFR, VEGFR, BRAF, and CDKs. Targeting folate-pathway enzymes (thymidylate synthase, DHFR) also disrupts nucleotide biosynthesis, and certain fused systems block tubulin polymerization to arrest mitosis. SAR studies highlight that electron-withdrawing groups (Cl, NO_2) at C-5 or C-6 enhance potency, whereas fused heterocycles (quinazoline, thienopyrimidine, pyridopyrimidine) improve bioavailability and selectivity. Hybrid molecules linking pyrimidine with triazoles, coumarins, or sulfonamides yield synergistic cytotoxic effects. Emerging strategies leverage covalent warheads at C-2/C-4 for irreversible enzyme engagement and N-linked linkers for PROTAC applications, underscoring the enduring versatility of the pyrimidine core in anticancer therapeutics.

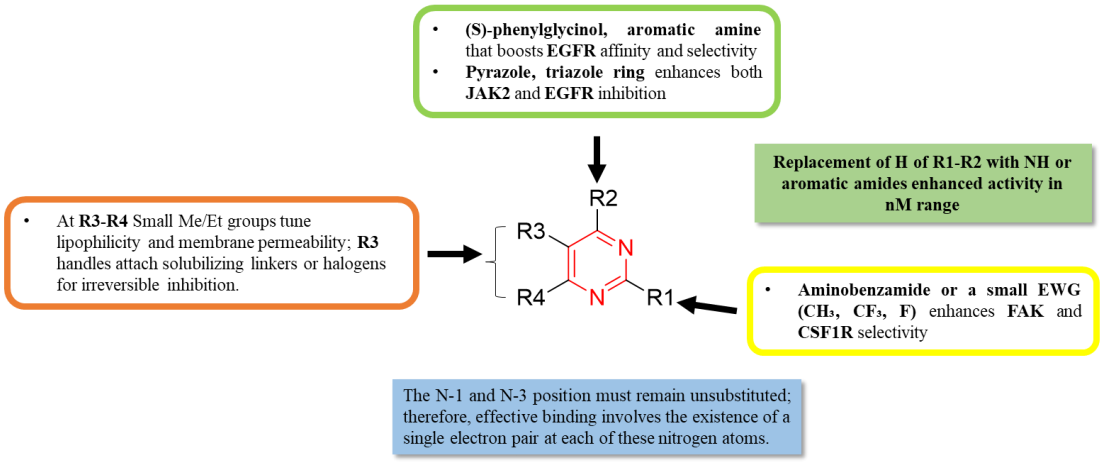

Figure 7: General SAR of pyrimidine as an anticancer agent.

Several pyrimidine-based compounds have advanced as potent anticancer agents, including 2,4-diaminopyrimidines that inhibit DHFR, and 4-anilinoquinazolines exemplified by clinically approved EGFR inhibitors erlotinib and gefitinib. Fused derivatives such as pyrimido[4,5-d]pyrimidines and thieno[2,3-d]pyrimidines have shown cytotoxicity across breast, colon, and lung cancer cell lines by targeting multiple kinases and inducing apoptosis. In vitro evaluations using human cancer cell lines like MCF-7, A549, HCT116, and HeLa have revealed promising compounds with low micromolar to nanomolar IC_{50} values. Select derivatives have also demonstrated significant tumor regression in animal models with manageable toxicity, underscoring their potential for clinical development.

5. Approved Drugs Based on Pyrimidine Core

Several clinically approved anticancer agents are based on the pyrimidine scaffold, highlighting its versatility and critical biological relevance. Among the most prominent is 5-fluorouracil (5-FU), a fluorinated uracil analog widely used in colorectal, breast, head and neck, and gastrointestinal cancers.[18] Its mechanism involves conversion into active metabolites that inhibit thymidylate synthase (TS) and incorporate into RNA and DNA, disrupting nucleic acid synthesis and function. Resistance to 5-FU commonly arises from TS upregulation and enhanced drug metabolism. [19] Capecitabine, an oral prodrug of 5-FU, offers improved tumor selectivity and reduced systemic toxicity by enzymatic conversion to 5-FU primarily within tumor tissue via thymidine phosphorylase, making it effective for metastatic breast and colorectal cancers.[20]

Gemcitabine, a difluoro analog of deoxycytidine, is effective against various solid tumors including pancreatic, lung, and bladder cancers. It acts by incorporating into DNA to cause chain termination and inhibiting ribonucleotide reductase, providing superior pharmacokinetics and tolerability compared to traditional pyrimidines.[21] Cytarabine (Ara-C), a cytidine analog with an arabinose sugar, is primarily used for hematologic malignancies such as acute myeloid leukemia. Its active triphosphate form inhibits DNA polymerase and incorporates into DNA, with high-dose regimens common during induction therapy.[22] Raltitrexed, structurally related to folic acid and pyrimidines, is a TS inhibitor used in colorectal cancer, especially in patients intolerant to 5-FU, functioning through direct TS inhibition to block DNA synthesis.[23] Lastly, pemetrexed, though folate-related, contains a pyrimidine-like

pharmacophore and is approved for malignant pleural mesothelioma and non-small cell lung cancer. It acts as a multi-targeted antifolate inhibiting TS, dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), all critical enzymes in nucleotide biosynthesis.[24] Together, these pyrimidine-based drugs exemplify diverse mechanisms of action and clinical applications, underscoring the scaffold's importance in anticancer therapy.

Table 1: Small molecule protein kinase inhibitors that have been approved by the USFDA.

Drug	Company	Primary targets	Year approved
Abemaciclib[25]	Lilly	CDK4/6	2017
Brigatinib[26]	Ariad Pharma	ALK; ROS1; IGF-1R; Flt3; EGFR	2017
Neratinib[27]	Puma Biotech	ErbB2/ HER2	2017
Encorafenib[28]	Array BioPharm	B-Raf	2018
Fostamatinib[29]	Rigel	SYK, Spleen tyrosine kinase	2018
Gilteritinib[30]	Astellas Pharma	Flt3	2018
Fedratinib[31]	Celgene	JAK2	2019
Avapritinib[32]	Blueprint Medi-cines Corp	PDGFR; Kit	2020
Pralsetinib[33]	Blueprint Medi-cines Corp	RET	2020
Infigratinib[34]	QED Thera.	FGFR2	2021
Mobocertinib[35]	Takeda Pharma	EGFR with exon 20 insertion	2021
Pacritinib[36]	CTI Bio-Pharma	JAK2	2022
Momelotinib[37]	GSK	JAK1/2	2023
Lazertinib[38]	Janssen	Mutant EGFR	2024
Tovorafenib[39]	Day One	B/C-Raf	2024

6. Recent Research Highlights

Recent advances in pyrimidine chemistry have yielded a host of novel analogues designed to overcome limitations in cytotoxicity, pharmacokinetics, and target selectivity. Hybrid molecules that fuse the pyrimidine core with other heterocycles such as triazoles and quinolines are garnering attention for their ability to engage multiple oncogenic pathways simultaneously.[40] Rigid, fused systems like

pyrimido[4,5-d]pyridazine and triazolopyrimidine scaffolds have demonstrated enhanced binding affinity for key cancer targets, while substituted pyrimidines aimed at epigenetic regulators promise to modulate gene expression in tumor cells.[41] Among the most noteworthy are pyrimidine–sulfonamide hybrids, which have shown potency against CDK2 and triggered apoptotic cascades in leukemia cell lines, and thienopyrimidines that act as dual inhibitors of EGFR and VEGFR, thereby combining antiangiogenic and antiproliferative effects. Nitro-pyrimidines, still in early stages, are being evaluated for their ability to generate reactive oxygen species and induce DNA strand breaks selectively in cancerous tissues.[42]

AI and in silico tools accelerate pyrimidine-based drug discovery by screening targets, using QSAR for SAR insights, and predicting pharmacokinetics to prioritize potent, selective anticancer candidates for synthesis.[43]

Pyrimidine scaffolds remain pivotal in oncology, with TAS-102 approved for colorectal cancer, tegafur showing improved tolerability in head and neck cancers, and RX-3117 in trials for lung and pancreatic cancers.[44–46] Novel pyrimidine formulations like liposomal 5-FU improve targeting and reduce toxicity. Patents cover kinase inhibitors, anti-mitotics, and hybrids.[47]

7. Challenges and Opportunities

Despite major advances in pyrimidine-based anticancer drug development, several critical challenges hinder their clinical translation. A key issue is drug resistance, which reduces the efficacy of commonly used analogs like 5-fluorouracil (5-FU) and gemcitabine. Resistance mechanisms include upregulation of target enzymes (e.g., thymidylate synthase), activation of efflux pumps (e.g., ABC transporters), enhanced DNA repair, and metabolic alterations. Many pyrimidines also suffer from poor selectivity, affecting healthy cells and causing off-target toxicities such as myelosuppression and hepatotoxicity, thereby limiting dose escalation and long-term use. Limited bioavailability of oral formulations, due to poor solubility and rapid metabolism, often necessitates higher dosing, increasing systemic toxicity.

Another major challenge is the synthetic complexity of functionalized or fused pyrimidine derivatives, which often require multi-step, low-yield reactions that are economically unsustainable for large-scale production. This also hampers reproducibility and scalability. Moreover, poor pharmacokinetics and inconsistent biological results contribute to a high attrition rate from preclinical success to clinical viability.

To overcome these barriers, green and scalable synthetic methods are being developed to improve sustainability and efficiency. Simultaneously, next-generation pyrimidine analogs are being tailored to target emerging pathways, such as epigenetic enzymes like HDACs and DNMTs. Covalent inhibitors with electrophilic pyrimidine cores and PROTACs using pyrimidine ligands for targeted protein degradation are gaining interest. Artificial intelligence (AI), machine learning, and molecular modeling are increasingly integrated into design workflows to predict activity, reduce toxicity, and optimize drug-like properties ushering in a more precise, data-driven era for pyrimidine-based anticancer therapy.

8. Conclusion

Pyrimidine derivatives continue to hold central importance in anticancer drug design, leveraging the scaffold's versatility to generate compounds with diverse mechanisms of action and favorable pharmacological profiles. Advances in synthetic methodologies—from classical condensations to green, microwave-assisted, and catalyst-promoted protocols—have expanded accessible chemical space while improving sustainability and scalability. Structure–activity relationship studies have identified key substituent effects at C-positions and N-atoms that fine-tune potency, selectivity, and pharmacokinetics. The clinical success of pyrimidine-based agents such as 5-FU, capecitabine, gemcitabine, and pemetrexed underscores the scaffold's translational impact. Emerging strategies, including covalent warheads, PROTAC constructs, and hybrid heterocyclic frameworks, promise to overcome resistance and target difficult oncogenic pathways. Integration of AI, in silico screening, and flow chemistry will further accelerate discovery and optimization. Nonetheless, challenges remain in addressing drug resistance mechanisms, reducing off-target toxicities, and streamlining the synthesis of complex, fused systems. Continued interdisciplinary efforts in green chemistry, computational modeling, and novel mechanism exploration are poised to usher in the next generation of pyrimidine-based anticancer therapeutics, combining enhanced efficacy with sustainable production methods.

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