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Review Article

Pyrimidine Derivatives: A Comprehensive Review of Synthetic Strategies, Biological Activities and In-Silico Studies

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ABSTRACT

The pyrimidine nucleus is a six-membered aromatic ring in which nitrogen occupies the 1 and 3 positions. It underlies cytosine, thymine and uracil, the building blocks of nucleic acids, and this natural pedigree has made it a favorite framework for medicinal chemists. Both simple and ring-fused pyrimidines show antibacterial, anticancer, antiviral, antitubercular, antifungal and anti-inflammatory properties, and a number of marketed drugs are built on them. The article covers four areas: (i) routes to the ring, from classical condensations to multicomponent, environmentally friendly and metal-catalyzed methods; (ii) the main therapeutic activities, with representative scaffolds, targets and approved drugs; (iii) trends in structure–activity relationships (SAR) at positions 2, 4, 5 and 6 and in fused systems; and (iv) the growing use of docking, molecular dynamics (MD), ADME/ADMET prediction and drug-likeness filters when designing leads. Studies from 2020 to 2026 receive most attention. The review closes with a critical discussion, a list of unresolved gaps and a look ahead. Overall, we argue that progress is most likely when efficient synthesis, thorough biological testing and computational models backed by experimental evidence are pursued together.

INTRODUCTION

1.1 Significance of the pyrimidine scaffold

Heterocycles containing nitrogen are among the scaffolds most often used in drug discovery, and pyrimidine is a prominent member of the group. Cytosine, thymine and uracil in DNA and RNA are pyrimidines, and the ring also appears in thiamine and in many natural products[1,2]. Because biological systems already contain proteins that recognize this motif, pyrimidine-containing molecules readily bind enzymes,

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receptors and nucleic acids, which is one explanation for the diversity of pharmacological effects described for them[3,4]. Review articles repeatedly mention anti-cancer, antibacterial, antifungal, antiviral, anti-inflammatory, antitubercular and antimalarial actions for these compounds[5–8]. Ring-fused pyrimidines deserve particular attention, since adding a second ring has been reported to modify potency. The resulting thiazolo-, pyrido-, pyrazolo- and thieno-pyrimidines frequently serve as bio-isosteres of purines[6,9].

1.2 Structure and numbering

Positions in the pyrimidine ring ($C_4H_4N_2$) are labelled N1, C2, N3, C4, C5 and C6 (Figure 1). Because the two nitrogen's draw electron density out of the ring, the system is π-deficient and C2, C4 and C6 are electron-poor. Nucleophilic substitution, for example the exchange of a chlorine atom for an amine, therefore occurs preferentially at these carbons. C5 retains more electron density than the other carbons, so electrophilic reactions such as halogenation and nitration take place there. Although C4 and C6 are interchangeable in the unsubstituted ring, they stop being equivalent when substituents are present or when another ring is fused on. This dependence of reactivity on position affects both the synthetic chemistry (Section 2) and the SAR (Section 4).

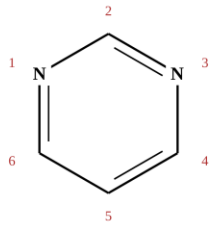


Figure 1: ***Structure and numbering of the pyrimidine ring.***

1.3 Scope of this review

The article is organized as follows. Section 2 deals with synthesis, Section 3 with biological activities, Section 4 with SAR and Section 5 with in-silico work. Section 6 summarizes advances made between 2020 and 2026, Section 7 offers a critical analysis, Section 8 lists research gaps, Section 9 outlines future directions and Section 10 concludes.

2. SYNTHETIC STRATEGIES

Pyrimidine syntheses can be placed in four groups: classical condensation reactions that form the ring, multicomponent and green procedures, functionalization of an existing ring with transition-metal catalysts, and annulation strategies that deliver fused systems[5,6] (Figure 2, Table 1).

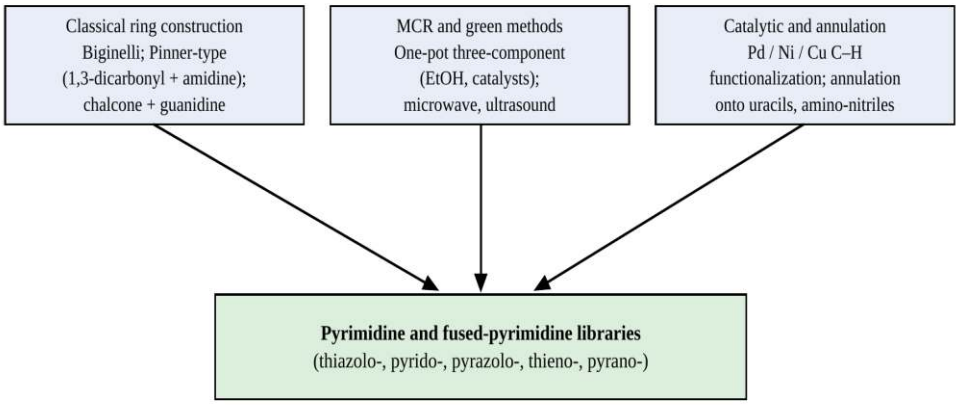


Figure 2: ***Main synthetic routes to pyrimidine and fused-pyrimidine libraries.***

2.1 Classical ring construction

Traditional approaches generally combine a three-carbon component with an N–C–N component such as urea, thiourea, guanidine or an amidine. Biginelli's reaction is the standard example: an aldehyde, a β-ketoester and urea or thiourea are heated together with an acid catalyst in a single pot, yielding 3,4-dihydropyrimidin-2 (1H)-ones or their thio analogues. Its scope and subsequent modifications have been reviewed at

length[10,11]. Pinner-type condensation of a 1,3-dicarbonyl compound with an amidine gives pyrimidines substituted at C2, while 4,6-diarylpyrimidines result when chalcones are cyclised with guanidine, urea or thiourea[5,8].

2.2 Multicomponent and green methods

In multicomponent reactions (MCRs), several reactants are assembled into the ring in one step with little waste. As an illustration, ethanol-based condensation of an aldehyde, a nitrile bearing an active methylene group and urea or thiourea has led to pyrimidine-5-carbonitriles, cyanothiouracils and pyrano-pyrimidines[7,8]. Current methods increasingly replace severe conditions with microwave or ultrasound heating, reusable catalysts and reactions without solvent[5].

2.3 Transition-metal-catalysed functionalization

Palladium, nickel and copper catalysts can modify a pyrimidine ring that has already been formed, without rebuilding it. One recent review compares such direct functionalization approaches and notes advantages in the number of steps, regiocontrol and ease of scale-up[12]. They are especially useful for adding diversity at a late stage, which helps when SAR libraries are being prepared.

2.4 Fused-pyrimidine systems

Two general tactics lead to fused pyrimidines. One builds a further ring on a pyrimidine whose neighbouring substituents are suitably reactive, as is the case for 6-aminouracils and thioxopyrimidines. The other forms the pyrimidine ring on a pre-existing heterocycle that carries an amino-carbonyl or amino-nitrile pair. Fused systems may be sorted according to the size of the new ring, anywhere from five to eight atoms[6]. Pyrazolo[3,4-d]- and pyrazolo[1,5-a]pyrimidines are of special importance as scaffolds for kinase inhibitors[13–15].

Table 1: Overview of Synthetic Strategies for Pyrimidine Scaffolds.

Strategy	Typical building blocks	Typical products	Ref.
Biginelli reaction	Aldehyde, β-ketoester, urea/thiourea	Dihydropyrimidinones / thiones	10,11
Pinner-type condensation	1,3-Dicarbonyl, amidine	2-Substituted pyrimidines	5
Chalcone cyclocondensation	Chalcone, guanidine/urea/thiourea	4,6-Diaryl-pyrimidines	8
Three-component nitrile route	Aldehyde, active methylene nitrile, (thio)urea	Pyrimidine-5-carbonitriles, cyanothiouracils	7,8
Metal-catalysed C–H functionalization	Pyrimidine core; Pd, Ni or Cu catalyst	Late-stage substituted pyrimidines	12
Annulation to fused systems	6-Aminouracils, thioxopyrimidines, aminonitriles	Thiazolo-, pyrido-, pyrazolo-, thienopyrimidines	6,13

3. BIOLOGICAL ACTIVITIES

Figure 3 gives an overview of the activity classes, and Table 2 collects representative marketed or clinical-stage drugs built on pyrimidine[3,5].

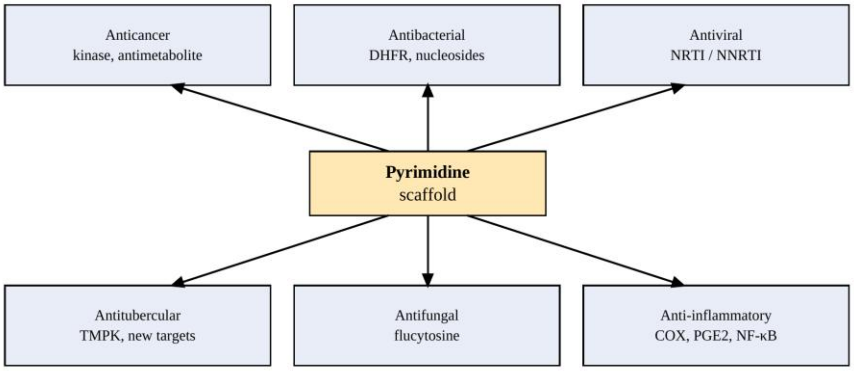


Figure 3: ***Major biological activities of pyrimidine derivatives, with example mechanisms or targets.***

3.1 Antibacterial activity

Antimicrobial resistance is a growing worldwide threat. A survey covering over 200 pyrimidines listed compounds with one to four substituents that display antimicrobial action; trimethoprim-type 2,4-diaminopyrimidine antifolates are among them[16]. Pyrimidines had already been described as bactericidal, fungicidal and virucidal agents in an earlier overview[4]. A review published in 2026 addresses pyrimidine nucleosides, sorting them into cytosine analogues and uracil/thymine analogues. To adjust target binding, passage through membranes and metabolic stability, chemists introduce modifications such as lipidation and selenylation. Because these molecules are prodrugs, intracellular phosphorylation is needed before they can interfere with nucleic acid synthesis. According to that review, translation to the clinic is held back by toxicity to the host, a narrow spectrum and scarce information on resistance[17].

3.2 Anticancer activity

Pyrimidine analogues were among the first rationally designed antimetabolites. The main actions of 5-fluorouracil are inhibition of thymidylate synthase and incorporation into RNA and DNA[18]; gemcitabine and cytarabine are further nucleoside antimetabolites of this type[12]. At present, however, most effort is directed at kinase inhibition. Approved kinase inhibitors with a pyrimidine or fused-pyrimidine core include imatinib, a phenylaminopyrimidine acting on BCR-ABL[19]; osimertinib, which inhibits EGFR including the T790M mutant[20]; and palbociclib, a pyrido[2,3-d]pyrimidine that blocks CDK4/6[21]. Roskoski has reviewed the properties of FDA-approved drugs in this class[22].

Because the pyrazolo[3,4-d]pyrimidine bicycle looks like the adenine ring of ATP, it can reproduce the contacts that ATP makes with the hinge region of kinases. Ibrutinib, a BTK inhibitor, is based on this core, and parsaclisib, sapanisertib and umbralisib are reported to have reached clinical trials[13]. Its isomer, pyrazolo[1,5-a]pyrimidine, has been tested against a wide range of targets such as CK2, EGFR, B-Raf, MEK, PDE4, BCL6, DRAK1, CDK1/2 and Pim-1[14]. More recent series cover thiazolo[4,5-d]pyrimidines (CDK, VEGFR, PI3K)[9], pyrido[2,3-d]pyrimidines (EGFR)[23], thieno-triazolopyrimidines (EGFR, PI3K)[24] and pyrimidine carboxylates (VEGFR)[25]. Among thiazolyl-pyrimidines designed against CK2α, five compounds had IC_{50} values between roughly 2.4 and 5.0 μM, whereas doxorubicin gave 6.18 μM in the same assay[26].

3.3 Antiviral activity

Nucleoside analogues based on pyrimidines are central to antiviral treatment. Zidovudine, an analogue of thymidine, was the first agent shown to block HIV replication in vitro[27]; overviews of nucleoside and non-nucleoside reverse-transcriptase inhibitors are available[28]. Rilpivirine, a diarylpyrimidine, illustrates that a pyrimidine scaffold without a sugar can also produce strong anti-HIV drugs[29]. Anti-HIV and other antiviral effects have also often been described for fused pyrimidines[6].

3.4 Antitubercular activity

Clinical progression of GSK 2556286, TBA-7371 and SPR720 stimulated interest in pyrimidines for tuberculosis. A recent review sorts pyrimidine-containing compounds by their targets and discusses SAR for each group[30]. In a distinct body of work, pyrimidine nucleosides and nucleotides were examined as inhibitors of thymidine monophosphate kinase from Mycobacterium tuberculosis (TMPKmt), with SAR and computational analysis in support[31].

3.5 Antifungal activity

Flucytosine (5-fluorocytosine) is the best-known pyrimidine antifungal. Fungal cells that are susceptible transform it into 5-fluorouracil, and one review is devoted to its pharmacology, clinical use and toxicity[32]. Wider reviews of the scaffold discuss other antifungal pyrimidines, among them fused ones[5,8].

3.6 Anti-inflammatory and other activities

Several mediators of inflammation, including prostaglandin E2, inducible nitric oxide synthase, TNF-α, NF-κB, leukotrienes and some interleukins, are thought to be suppressed by anti-inflammatory pyrimidines, either at the level of expression or of activity. The SAR of these compounds was analysed systematically in a 2021 review[33]. COX-1 and COX-2 are inhibited by some pyrimidines, and pyrimidine acrylamides have been put forward as starting points for antioxidants[12]. Antimalarial, anticonvulsant, antihypertensive and other effects have been reported too[6,7].

Table 2: Representative Marketed Pyrimidine-Based Drugs and Activities.

Drug / class	Pyrimidine type	Activity and target	Ref.
5-Fluorouracil	Pyrimidine antimetabolite	Anticancer; thymidylate synthase inhibition	18
Imatinib	Phenylaminopyrimidine	Anticancer; BCR-ABL kinase	19
Osimertinib	Anilinopyrimidine	Anticancer; EGFR (incl. T790M)	20
Palbociclib	Pyrido[2,3-d]pyrimidine	Anticancer; CDK4/6	21
Ibrutinib	Pyrazolo[3,4-d]pyrimidine	B-cell cancers; covalent BTK inhibitor	13
Zidovudine	Thymidine analogue	Antiviral; HIV reverse transcriptase	27
Rilpivirine	Diarylpyrimidine (DAPY)	Antiviral; HIV NNRTI	29
Trimethoprim-type	2,4-Diaminopyrimidine	Antibacterial; dihydrofolate reductase	16
Flucytosine	5-Fluorocytosine	Antifungal; converted to 5-FU in fungal cells	32

4. STRUCTURE–ACTIVITY RELATIONSHIP (SAR)

How SAR in pyrimidines plays out depends on the target and the chemical series, but the literature reveals several repeating trends (Figure 4, Table 3). Fusing a ring is the most widely applicable design tool; a review of ring-fused pyrimidines points out that fused systems frequently show additive effects on biological efficacy compared with the parent ring[6].

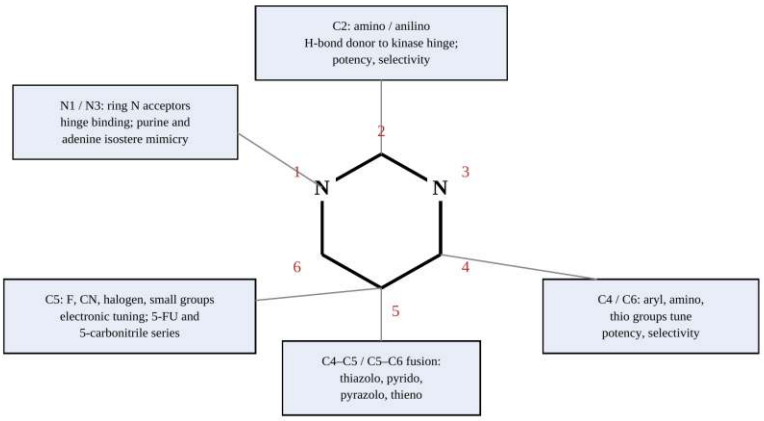


Figure 4: ***SAR map of the pyrimidine ring showing common substituent effects reported in the literature.***

In kinase inhibitors the ring nitrogens, together with an amino group, usually hydrogen-bond to the hinge region; imatinib and osimertinib, both 2-anilinopyrimidines, are examples of this binding mode[19,20]. For pyrazolo[3,4-d]pyrimidines, changing groups at N1, C3, C4 and C6 shifts kinase selectivity. A thiophenethyl group at C6 was required for anticancer potency in one CDK2 series, while the substitution on the C4-aryl group determined CDK2 inhibition[13]. At C5, fluorine characterises the antimetabolites 5-fluorouracil and flucytosine[18,32], and a carbonitrile group defines another family of anticancer, antimicrobial and antitubercular compounds[7]. Detailed SAR work on anti-inflammatory pyrimidines has pinpointed substitution patterns that strengthen COX or mediator inhibition without raising toxicity[33].

Table 3: Position-By-Position SAR Trends in Pyrimidine Derivatives.

Position	Common substituents	Typical effect	Ref.
N1 / N3	Ring nitrogens (acceptors); fused-ring N	Hinge binding; adenine/purine mimicry	13
C2	Amino, anilino, thio, alkoxy	H-bond donor/acceptor; potency and selectivity	19,20
C4 / C6	Aryl, anilino, amino, thioether	Potency, selectivity; CDK2 SAR depended on C4-aryl and C6 group	13
C5	F, CN, halogen, small alkyl	Electronic tuning; antimetabolite and 5-CN series	7,18
C4–C5 / C5–C6 (fusion)	Thiazolo, pyrido, pyrazolo, thieno, pyrano	Additive effect on bio-efficacy; kinase scaffolds	6,14

5. IN-SILICO STUDIES

Computational methods now routinely accompany synthesis and biological testing: they help refine pharmacophores, rank candidates and explain observed activity[34]. Figure 5 shows a typical workflow, and Table 4 lists representative studies.

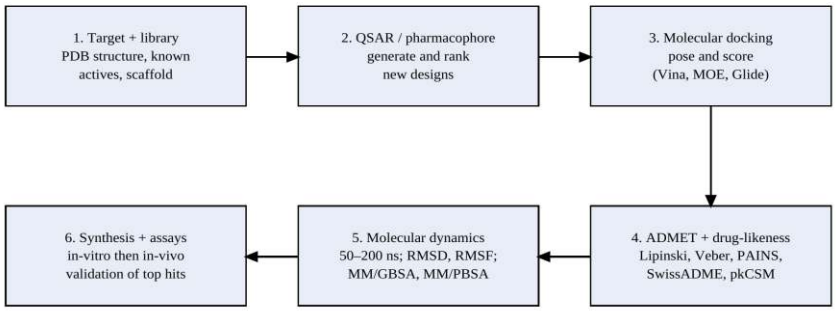


Figure 5: ***Typical integrated in-silico workflow for designing pyrimidine leads.***

5.1 Molecular docking

Docking predicts how a ligand sits in a protein binding site and how strongly it binds, making it the main technique of structure-based design[35]. Programs in common use are AutoDock Vina[36], the Molecular Operating Environment (MOE) and Schrödinger Maestro. Published pyrimidine studies include thiazolopyrimidines docked to CDK1, VEGFR-2 and PI3Kα[9], pyrido[2,3-d]pyrimidines to EGFR[23], pyrimidine carboxylates to VEGFR using MOE[25], and thiazolyl-pyrimidines to CK2α, where docking agreed with in-vitro cytotoxicity[26].

5.2 Molecular dynamics

Since docking usually holds the protein almost rigid, MD simulations with explicit solvent are used to see whether a docked complex remains stable[37], and GROMACS is a popular engine for this[38]. The usual results are RMSD, RMSF, hydrogen-bond occupancy and binding free energies by MM/GBSA or MM/PBSA. Examples include a 100-ns run with MM/PBSA on pyrimidine FAK inhibitors suggested by 3D-QSAR[39], a 100-ns run with MM/GBSA backing a pyrimidine-2,4-dione thymidylate synthase inhibitor[40], and 200-ns runs on thieno[2,3-d]pyrimidine cholinesterase inhibitors[41].

5.3 ADME/ADMET prediction

Absorption, distribution, metabolism, excretion and toxicity are usually predicted with free tools such as SwissADME[42] and pkCSM[43]. ADMET analysis of pyrido[2,3-d]pyrimidine EGFR candidates showed they obeyed Lipinski's rule, had no PAINS or Brenk alerts (unlike erlotinib) and were predicted to be well absorbed from the gut[23]. Good oral bioavailability was likewise predicted for thiazolyl-pyrimidines[26].

5.4 Drug-likeness

Lipinski's rule of five[44] and the Veber criteria, which concern polar surface area and the number of rotatable bonds[45], are used to judge drug-likeness; PAINS filters add to these by removing chemotypes that tend to interfere with assays[46]. Earlier in the process, QSAR and pharmacophore models[47] propose new structures. A Maestro-based study found that 43 pyrimidine derivatives cleared ADMET screening, three of which were predicted to bind DNA most tightly[34].

Table 4: Representative In-Silico Studies of Pyrimidine Derivatives.

Scaffold / study	Target	Methods	Ref.
Thiazolopyrimidines	CDK, VEGFR, PI3K	Docking, Lipinski, ADMET	9
Pyrido[2,3-d]pyrimidines	EGFR	Docking, ADMET (Lipinski, PAINS/Brenk)	23
Thiazolyl-pyrimidines	CK2α	In-vitro assay, docking, ADMET	26
Thieno-triazolopyrimidines	EGFR, PI3K	Docking, in-silico ADME	24
Pyrimidine carboxylates	VEGFR	Docking (MOE), ADMET	25
Pyrimidine DNA inhibitors	DNA	Pharmacophore, 3D-QSAR, docking, ADME	34
Pyrimidine Schiff bases	Cancer cell lines	Gaussian, Maestro docking, ADME/T	48
Pyrimidine FAK inhibitors	FAK	3D-QSAR, docking, 100-ns MD, MM/PBSA	39
Pyrimidine-2,4-diones	Thymidylate synthase	Docking, 100-ns MD, MM/GBSA, ADMET	40

Scaffold / study	Target	Methods	Ref.
Thieno[2,3-d]pyrimidines	AChE / BChE	Docking, 200-ns MD, MM/GBSA	[41]
Benzimidazo-pyrimidines	α-Glucosidase	QSAR, docking, ADMET, MD	[49]

6. RECENT ADVANCES (2020–2026)

Kinase-focused scaffolds. A review from 2020 follows the maturation of pyrazolo[3,4-d]pyrimidines, covering ibrutinib-derived covalent BTK inhibitors and BTK-targeting PROTACs intended to circumvent mutation of the reactive cysteine[13]. A 2025 review treated pyrazolo[1,5-a]pyrimidines as protein kinase inhibitors across at least nine kinase families[14].

Anti-infectives. Clinical trials have been reached by pyrimidine-based antitubercular compounds[30], and in view of antimicrobial resistance pyrimidine nucleosides are again being considered as antibacterial leads[17].

Inflammation and synthesis. The SAR of anti-inflammatory pyrimidines was brought together in 2021[33], and a 2025 review covered direct functionalization chemistry[12].

New anticancer series. Pyrido[2,3-d]pyrimidine EGFR inhibitors (2026)[23] and thiazolyl-pyrimidines active on CK2α (2025)[26] typify what is now a standard pipeline: synthesis, assay, docking and ADMET prediction.

Wider indications and longer simulations. Dual cholinesterase inhibitors for Alzheimer's disease, supported by 200-ns MD[41], and α-glucosidase inhibitors studied by QSAR, docking, ADMET and MD[49] show that pyrimidine design is moving into new areas; thymidylate synthase inhibitors are being developed using 100-ns MD as well[40].

7. CRITICAL ANALYSIS

Potency versus cellular activity. IC_{50} values from enzyme assays predict cellular efficacy poorly. In a set of BTK inhibitors derived from ibrutinib, a vinyl sulfonamide with a lower enzyme IC_{50} than ibrutinib had no useful antiproliferative activity in two B-cell leukaemia lines, but an acetamide analogue that was weaker against the enzyme killed cells at low micromolar concentrations[13]. Relying on a single enzyme assay for optimisation may thus mislead.

Selectivity and safety. Kinases have very similar ATP sites, which makes selectivity a constant problem. Ibrutinib is only moderately selective, and its off-target toxicity has been connected to a conserved cysteine that other kinases also carry; in the MER-inhibitor series, hERG liabilities forced redesign as well[13].

Comparisons and controls. Whether new compounds beat a reference drug such as doxorubicin[26] depends on cell line, exposure time and assay format. IC_{50} values or docking scores from different papers cannot be compared directly when the software, force fields and protein structures differ.

Predictive tools are hypotheses. Docking, ADMET web servers and rule-based filters[42–44] are cheap but only approximate. Obeying Lipinski's rule or showing no PAINS alerts guarantees neither oral bioavailability nor safety. MD adds rigour, yet simulations of 100–200 ns are brief compared with many binding events, and several reports use only one replica.

Translational gap. A large share of pyrimidine studies end with cytotoxicity in cell lines and computational ranking. Nucleoside antibacterials, by contrast, are openly acknowledged to face unresolved clinical barriers in host toxicity and narrow spectrum[17].

8. RESEARCH GAPS

- Experimental binding evidence (crystallography, SPR, thermal-shift assays) or in-vivo pharmacokinetics is seldom combined with in-silico predictions.
- Little is known about resistance to pyrimidine nucleosides, and mechanistic work seldom looks beyond nucleic acid synthesis[17].
- Controls, cell lines, docking protocols and numbers of MD replicates are described inconsistently, so meta-analysis is not possible.
- The range of targets is limited: most recent studies go back to EGFR, VEGFR, CDK and PI3K, leaving pyrimidine-biosynthesis targets in pathogens and antitubercular targets with little chemical precedent largely unexplored[30,31].

- Although greener routes are often claimed, green-chemistry metrics are seldom given for pyrimidine syntheses[5].

9. FUTURE PERSPECTIVES

- **Targeted protein degradation.** BTK-directed PROTACs based on a pyrazolo[3,4-d]pyrimidine core demonstrate that degraders can overcome resistance arising from cysteine mutation[13].
- **Covalent and multi-target design.** Covalent warheads and dual- or multi-kinase profiles, steered by kinome-wide selectivity screening[13,14].
- **Nucleoside prodrugs.** Antibacterial pyrimidine prodrugs designed around activating enzymes, together with combination therapy to extend the spectrum[17].
- **Validated computational pipelines.** Workflows connecting QSAR, docking, replicated MD with free-energy calculations and ADMET, with experimental confirmation to follow[37,39,49].
- **Sustainable synthesis.** Catalytic C–H functionalization and multicomponent routes, reported together with green metrics[5,12].

CONCLUSION

Pyrimidine remains among the most fruitful scaffolds in drug discovery, resting on well-established synthetic chemistry, drugs already validated in the clinic and abundant SAR knowledge. Computational tools speed up the identification of leads, but they are only as useful as the experimental validation and consistent reporting behind them. Future progress will probably come from selective and covalent kinase chemistry, nucleoside prodrugs for infections, targeted degradation and computational pipelines that are rigorously validated.

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[Authors to add acknowledgment, if any.]

CONFLICT OF INTEREST

[Authors to declare any conflicts of interest, or state that there are none.]

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