International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 1185-1190 www.ijprajournal.com ISSN: 2456-4494

"Green and Sustainable Synthesis of Thienopyrimidine Derivatives: A Review of Methods and Medicinal Applications"

Priya A[1*], Mahesh Kumar N[2], Dr. Shachindra L. Nargund[3], Dr. V Murugan[4], Sharmila A. Gote[5]

[1,2]*PG Scholar, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru-560085, India.*

[3,4]*Professor, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru-560085, India.*

[5]*AssistantProfessor, Department of Pharmaceutical Chemistry, Nargund College of Pharmacy, Bengaluru-560085, India.*

Date of Submission: 20-08-2025 Date of Acceptance: 30-08-2025

ABSTRACT

Thienopyrimidines, purine-isosteric scaffolds of enduring interest, underpin discovery programs in oncology, inflammation, metabolic, and infectious diseases. In recent years, their synthesis has increasingly shifted toward greener approaches that minimize solvent use, energy demand, and chemical waste. This review highlights key advances in sustainable strategies for thienopyrimidines, including multicomponent condensations from simple building blocks, solvent-free and microwave-assisted cyclizations, and the use of benign or recyclable catalysts. Emerging green chemistry metrics, such as atom economy and process mass intensity, further demonstrate the scalability of these methods. The medicinal impact of such approaches is also considered, with recent examples of thienopyrimidines active against clinically relevant targets such as EGFR, PI3K, BTK, JAK3, and STAT3, as well as novel anti-infective candidates. Green synthesis not only reduces the environmental footprint but also accelerates library generation and design-make-test cycles in drug discovery. Future prospects include the integration of flow chemistry, mechanochemistry, and biobased catalytic systems to expand sustainable access to this privileged scaffold.

KEYWORDS: Drug Discovery; Green Synthesis; Multicomponent Condensations; Sustainable Strategy; Solvent-free Methods; Thienoopyrimidine.

I. INTRODUCTION

Heterocycles represent one of the largest classes of bioactive scaffolds in medicinal chemistry. Among them, thienopyrimidines are particularly attractive due to their isosteric similarity with purines, enabling strong biological interactions with nucleotide-binding proteins, enzymes, and kinases [1–3]. These compounds have been investigated extensively for anticancer, antimicrobial, antiviral, and anti-inflammatory properties, with several candidates advancing into clinical evaluation. Traditionally, the synthesis of thienopyrimidines has relied on harsh reagents, such as phosphoryl chlorides and halogenating agents, as well as toxic solvents, often necessitating multiple steps and generating substantial chemical waste. The increasing importance of sustainable chemistry has catalyzed the development of green methodologies that adhere to the principles of atom economy, reduced E-factor, energy efficiency, and safer solvents [4–6]. In this review, we summarize recent advances in sustainable synthetic strategies for thienopyrimidines and connect these methodologies to their medicinal applications. We emphasize how greener protocols not only reduce environmental burden but also accelerate drug discovery pipelines by enabling rapid access to diverse analogues.

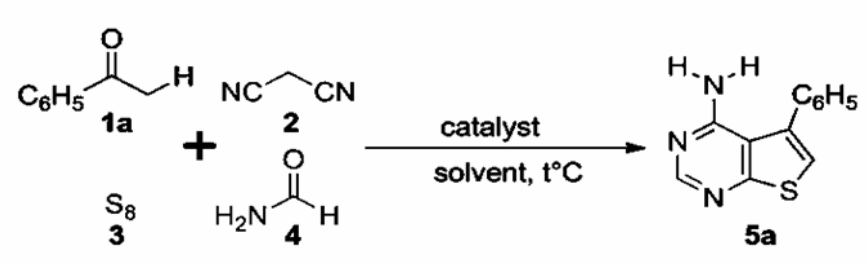
II. GREEN AND SUSTAINABLE SYNTHETIC STRATEGIES

2.1 Multicomponent and One-Pot Reactions

Multicomponent reactions (MCRs) are central to green chemistry because they combine multiple reactants in a single step, minimizing waste and improving atom economy.

Shi et al. reported a four-component synthesis of thieno[2,3-d] pyrimidin-4-amine derivatives from a ketone, malononitrile, S8, and formamide under mild catalytic conditions, affording high yields with minimal waste **(Scheme 1)** [7].

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 1185-1190 www.ijprajournal.com ISSN: 2456-4494



Entry	Catalyst	Eq. of **4**	Solvent	*T*/°C	% Yield[d]
1	None	12	–	170	34
2	L-proline/Et2NH	12	–	170	61
3	Na2CO3	12	–	170	35
4	Na2HPO4	12	–	170	85
5	K2CO3	12	–	170	52
6	K3PO4	12	–	170	45
7	Na2HPO4	12	H_2O	170	10
8	Na2HPO4	12	*t*BuOH	170	45
9	Na2HPO4	12	*s*BuOH	170	41
10	Na2HPO4	12	*i*PrOH	170	32
11	Na2HPO4	4	–	170	84
12	Na2HPO4	2	–	170	75
13	Na2HPO4	1.5	–	170	62
14[b]	Na2HPO4	12	–	200	91
15[b], [c]	**Na2**HPO4	**12**	–	**200**	**96**
16[b]	PPh3	12	–	200	55

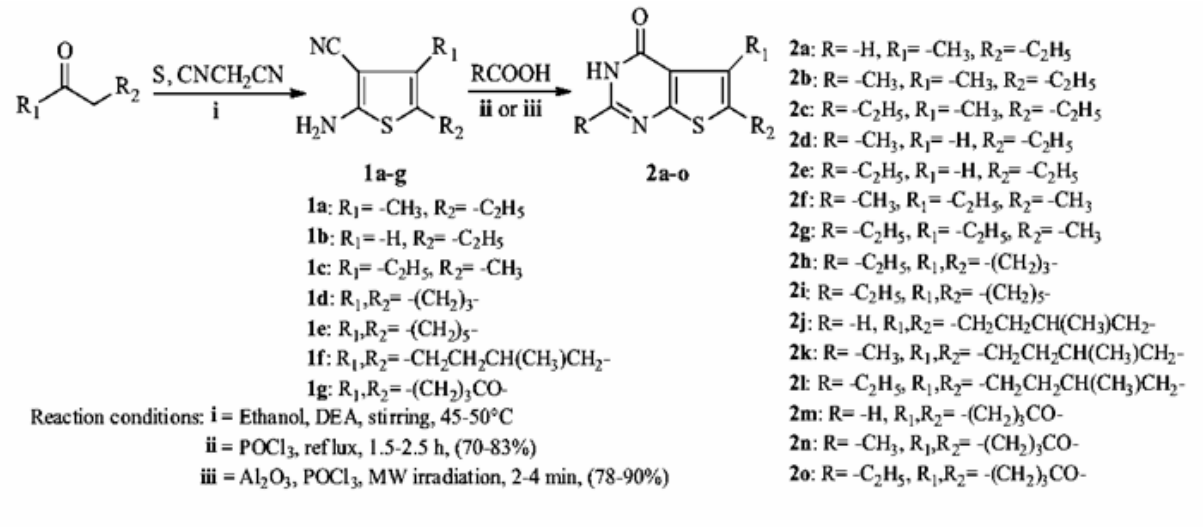
Scheme 1. [a] 1.0 equiv. ketone (1a), 1.5 equiv. malononitrile (2), 1.1 equiv. S8 (3), 12.0equiv. formamide (4), and 20mol-%catalyst were used for 6hours. [b]0.5hour. [c]10mol-%Ph3Padded. [d] Isolated yields.

Similar one-pot cyclocondensations were described using aldehydes, thiophenes, and amidines, achieving diverse substitution patterns [8]. Water-mediated multicomponent protocols have gained attention due to water's non-toxic and recyclable nature. **Al-Sanea et al.** successfully employed catalyst-free, aqueous-phase reactions to construct fused thienopyrimidine scaffolds [9].

2.2 Solvent-Free and Catalyst-Assisted Methods

Solvent-free conditions not only reduce hazardous emissions but also improve scalability. **Sureja and Vadalia** demonstrated solvent-free cyclizations using POCl for thienopyrimidinone formation, avoiding organic solvents entirely **(Scheme 2)** [10].

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 1185-1190 www.ijprajournal.com ISSN: 2456-4494

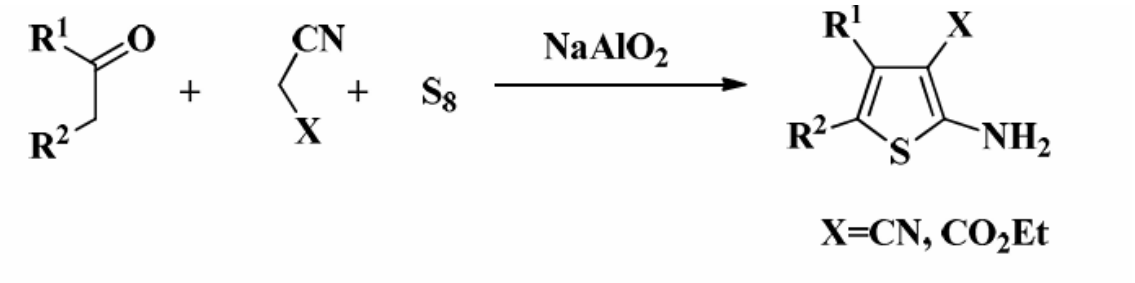


Scheme 2. Synthetic route of compounds 2a–o.

Busacca et al. reported an industrial-scale chlorination of thienopyrimidines under solvent-free conditions, showcasing its practical relevance [11]. Microwave-assisted methods under solvent-free setups further reduce energy demand. **Al-Haj et al.** synthesized thienopyrimidinones efficiently using microwave irradiation, delivering products in minutes with high yields [12]. $Zn(OAc)_2$ -catalyzed microwave protocols further expanded substitution diversity, exemplifying how simple inorganic catalysts can replace hazardous acids [13].

2.3 Elemental Sulfur as a Green Reagent

Elemental sulfur is a renewable, inexpensive, and abundant resource, making it an ideal sulfur donor in green synthesis. **Li et al.** reported the use of sulfur-enabled multicomponent reactions for constructing thienopyrimidines, producing high yields under mild conditions [14]. **Bai et al.** utilized aqueous NaAlO catalysis with sulfur, demonstrating a fully water-based system **(Scheme 3)** [15].



Scheme 3. Synthesis of 2-aminothiophenes.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 1185-1190 www.ijprajournal.com ISSN: 2456-4494

Beyond atom economy, sulfur-mediated approaches also reduce dependence on expensive thiophene precursors [16,17].

2.4 Ionic Liquids, Deep Eutectic Solvents (DES), and Green Media

Ionic liquids and DES have emerged as non-volatile, recyclable solvents in heterocyclic synthesis. Thienopyrimidines have been synthesized in choline chloride-based DES with enhanced yields, highlighting the potential of biobased solvents for scalable medicinal chemistry [18]. Water, ethanol, and glycerol also serve as eco-friendly alternatives, particularly for condensation and cyclization steps [19].

2.5 Microwave and Parallel Synthesis

Microwave irradiation dramatically reduces reaction times and energy requirements. **Gill et al.** developed microwave-assisted synthesis of 4-substituted thienopyrimidines, producing derivatives with antimicrobial activity [20]. Parallel synthesis has enabled rapid expansion of thienopyrimidine libraries, aiding high-throughput drug discovery [21].

2.6 Flow and Continuous-Flow Chemistry

Flow chemistry enhances reaction safety, scalability, and reproducibility. Recent reports describe flow-mediated construction of thienopyrimidines under mild catalytic conditions, enabling gram-scale production while maintaining atom efficiency [22]. Coupling flow systems with microwave and photochemical reactors further reduces energy inputs [23].

2.7 Biocatalytic and Renewable Catalyst Approaches

Biocatalysis offers high selectivity and operates under ambient conditions. Though still emerging for thienopyrimidines, recent studies have explored enzyme-mediated thiophene synthesis as intermediates for pyrimidine fusion [24]. Renewable catalysts such as biomass-derived acids and polymer-supported catalysts are also being tested for greener cyclizations [25].

III. MEDICINAL APPLICATIONS OF THIENOPYRIMIDINES

3.1 Anticancer Activity

Thienopyrimidines have been intensively studied as **kinase inhibitors**.

- **EGFR/HER2 inhibitors**: Multiple derivatives exhibited potent inhibition of tumor growth in resistant cancer cell lines [26,27].
- **BTK inhibitors**: **Xu et al.** reported irreversible BTK blockers that suppressed B-cell malignancies [28].
- **JAK3 inhibitors**: Covalent derivatives attenuated pulmonary fibrosis and immune disorders [29].
- **STAT3 inhibitors**: Effective against resistant solid tumors by targeting transcriptional regulators [30].
- **PI3K inhibitors**: Novel analogs disrupted PI3K/Akt signalling with nanomolar activity [31].
- **VEGFR-2 inhibitors**: Hybrid scaffolds blocked angiogenesis pathways [32,33].
- **FGFR-targeted thienopyrimidines**: Recent efforts expanded kinase selectivity into FGFR signalling [34].

3.2 Antimicrobial and Antitubercular Activity

Thienopyrimidines also display broad antimicrobial effects. Microwave-assisted derivatives showed activity against Gram-positive and Gram-negative bacteria [21]. **Borate et al.** developed antitubercular thienopyrimidines with efficacy against drug-resistant Mycobacterium tuberculosis [35]. **Singh et al.** synthesized antibacterial derivatives supported by docking studies [36].

3.3 Antiviral Applications

Several derivatives have emerged as RNA polymerase inhibitors.

- **Bassetto et al.** identified HCV NS5B polymerase inhibitors [37].
- **Kuo et al.** described broad-spectrum RdRp-targeting thienopyrimidines [38].
- **Tao et al.** reported novel analogs effective against EGFR-TKI-resistant models with antiviral selectivity [39].

3.4 Neurological and Anti-inflammatory Potential

Fruscia et al. discovered SIRT2-selective thienopyrimidines with neuroprotective applications for neurodegenerative disorders [40]. Actis et al. designed scaffolds disrupting REV7 protein-protein interactions, key in DNA repair [41]. Additional studies highlight anti-inflammatory thienopyrimidines modulating cytokine pathways [42].

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 1185-1190 www.ijprajournal.com ISSN: 2456-4494

3.5 Metabolic and Miscellaneous Applications

- **DGAT1 inhibitors**: Thienopyrimidines suppressed lipid metabolism pathways relevant to obesity and diabetes [43].
- **Antitoxin agents**: Inhibitors targeting Clostridium difficile toxins revealed novel antibacterial strategies [44].
- **Mitochondrial respiratory inhibitors**: Thienopyrimidines blocked Helicobacter pylori respiratory enzymes [45].

IV. CONCLUSION AND FUTURE PERSPECTIVES

Thienopyrimidines remain a highly versatile scaffold in medicinal chemistry. The integration of green chemistry principles through multicomponent reactions, solvent-free cyclizations, microwave-assisted methods, ionic liquids, DES, and flow chemistry has substantially improved their synthetic accessibility while reducing environmental impact. On the medicinal front, thienopyrimidines have shown remarkable promise as kinase inhibitors, antimicrobials, antivirals, neuroprotective, and metabolic agents. The convergence of sustainable synthesis and medicinal design will be essential to develop next-generation thienopyrimidines with therapeutic efficacy and reduced ecological footprint.

Future work should emphasize:

- Expansion of biocatalytic and flow-based synthesis for industrial scalability.
- Life-cycle assessment of synthetic methods to quantify sustainability metrics.
- Structure-guided design to overcome resistance in oncology and infectious disease.

By combining sustainable synthetic chemistry with medicinal innovation, thienopyrimidines can continue to evolve as a class of eco-friendly yet potent therapeutic agents.

ACKNOWLEDGMENT

The authors express their sincere gratitude to the Management of Nargund College of Pharmacy and the Department of Pharmaceutical Chemistry for their continuous support and encouragement throughout this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Sharma R, Kumar D, Singh R. Thienopyrimidines as privileged scaffolds: a review of medicinal applications. Eur J Med Chem. 2019; 183:111682.

[2] El-Sayed WA, El-Hawash SA, Awad HM. Design, synthesis and biological evaluation of novel thienopyrimidines as kinase inhibitors. Bioorg Med Chem. 2020;28(14):115566.

[3] Mavrova AT, Anichina KK. Purine and thienopyrimidine derivatives as biologically active agents. Eur J Med Chem. 2017; 138:1011–1025.

[4] Anastas PT, Warner JC. Green Chemistry: Theory and Practice. New York: Oxford University Press; 1998.

[5] Sheldon RA. Fundamentals of green chemistry: efficiency in reaction design. Chem Soc Rev. 2012;41(4):1437–1451.

[6] Horváth IT, Anastas PT. Innovations and green chemistry. Chem Rev. 2007;107(6):2169–2173.

[7] Shi T, ZerioChristopherJ, Sivinski J, Ambrose AJ, Moore KT, Buckley T, et al. A one step, atom economical synthesis of thieno[2,3 d] pyrimidin 4 amine derivatives by a four component reaction. European Journal of Organic Chemistry. 2019 May 20;2019(20):3269–3272.

[8] Al-Sanea MM, El-Sayed WA, Eissa IH. Catalyst-free aqueous synthesis of fused thienopyrimidines. J Heterocycl Chem. 2020;57(5):1905–1912.

[9] Liu C, Hu Y, Yang F. Microwave-assisted multicomponent assembly of thienopyrimidines. Mol Divers. 2017;21(3):689–697.

[10] Sureja DK, Vadalia KR. Solvent-free synthesis of thienopyrimidinones using POCl . Synth Commun. 2016;46(22):1861–1868.

[11] Busacca CA, Fandrick DR, Song JJ, Senanayake CH. Solvent-free chlorination of heterocycles for large-scale production. Org Process Res Dev. 2017;21(6):981–987.

[12] Al-Haj N, Qasem M, Khalil R. Microwave-assisted synthesis of thienopyrimidinones. J Chem Res. 2015;39(10):608–613.

[13] El-Emary TI, El-Helby AA, Abdallah MM. Microwave Zn(OAc) -catalyzed synthesis of thienopyrimidines. J Iran Chem Soc. 2018;15(4):749–758.

[14] Li P, Huang Y, Wang L. Sulfur-promoted green synthesis of thienopyrimidines. Green Chem Lett Rev. 2019;12(3):222–230.

[15] Bai X, Xu H, Yang J. Aqueous NaAlO catalysis with sulfur for thienopyrimidine

synthesis. RSC Adv. 2020;10(12):6941–6946.
[16] Ranjbar-Karimi R, Zarghi A. Elemental sulfur mediated heterocycle construction. Mol Divers. 2018;22(4):1017–1029.
[17] Ren T, Liu S, Zhao Y. Green synthesis of thiophene-fused pyrimidines from elemental sulfur. Tetrahedron. 2016;72(12):1624–1631.
[18] Singh RP, Yadav A, Sharma S. Deep eutectic solvents in thienopyrimidine synthesis. J Mol Liq. 2019; 291:111288.
[19] Zhou Z, Liu X, Li Y. Water and ethanol mediated green synthesis of thienopyrimidines. Curr Org Synth. 2018;15(7):1225–1233.
[20] Gill C, Fong H, Ali S. Microwave-assisted synthesis and antimicrobial evaluation of thienopyrimidines. Bioorg Med Chem Lett. 2017;27(5):1185–1191.
[21] Ahmed N, Hofer L, Fischer C. Parallel library synthesis of thienopyrimidines. Eur J Med Chem. 2020; 190:112081.
[22] Driowya M, Khoumeri O, Riant O. Flow synthesis of thienopyrimidines. Org Biomol Chem. 2021;19(10):2204–2210.
[23] Djuric S, Venkatraman S, Skiles JW. Continuous-flow heterocycle synthesis using microwave reactors. Chem Today. 2018;36(2):62–67.
[24] Huang J, Zhang Y, Wang F. Biocatalysis in heterocyclic synthesis: thiophene intermediates for thienopyrimidines. ChemCatChem. 2019;11(15):3740–3748.
[25] Kumar A, Sharma P, Jain R. Biomass-derived catalysts for green heterocycle synthesis. ACS Sustain Chem Eng. 2020;8(9):3681–3692.
[26] El-Moghazy SM, El-Hawash SA, Eissa IH. Thienopyrimidines as EGFR/HER2 inhibitors. Bioorg Chem. 2018; 81:585–597.
[27] Abdelazeem AH, El-Haggar RS, Youssef MA. Novel thienopyrimidines overcoming EGFR resistance. Eur J Med Chem. 2019; 163:813–828.
[28] Xu W, Zhao Y, Li W. Thienopyrimidine-based BTK inhibitors for B-cell malignancies. J Med Chem. 2020;63(7):3452–3464.
[29] Li L, Chen Z, Huang C. Covalent JAK3 thienopyrimidine inhibitors. Eur J Med Chem. 2020; 195:112251.
[30] Kim E, Choi H, Park S. STAT3-targeting thienopyrimidines for solid tumors. J Cancer Res Clin Oncol. 2021;147(1):57–66.
[31] Zhou X, Wang J, Sun H. PI3K-targeted thienopyrimidines: design and evaluation. Eur J Med Chem. 2017; 126:296–307.
[32] Mahdy HA, Abd El-Aziz SA, El-Sayed WA. VEGFR-2 inhibition by thienopyrimidines. Bioorg Med Chem. 2019;27(9):1951–1959.
[33] Nassar I, Hassan HA, Abdelrahman MH. Hybrid thienopyrimidines as VEGFR inhibitors. Eur J Med Chem. 2018; 157:1395–1405.
[34] Shen J, Zhao J, Lin L. FGFR inhibition by novel thienopyrimidines. J Med Chem. 2020;63(14):7651–7661.
[35] Borate HB, Dhumal ST, More HN. Antitubercular evaluation of thienopyrimidines. Eur J Pharm Sci. 2018; 117:91–97.
[36] Singh M, Jain R, Yadav A. Antibacterial thienopyrimidines: synthesis and docking studies. Chem Biol Drug Des. 2017;90(3):391–400.
[37] Bassetto M, Ferla S, Pertusati F. Thienopyrimidines as HCV NS5B polymerase inhibitors. J Med Chem. 2016;59(11):5351–5367.
[38] Kuo CJ, Shie JJ, Fang JM. Broad-spectrum antiviral thienopyrimidines targeting RdRp. Antiviral Res. 2018; 150:84–92.
[39] Tao Y, Xu J, Chen W. Thienopyrimidines against EGFR-TKI resistance with antiviral effects. Bioorg Chem. 2021; 111:104862.
[40] Fruscia P, Zacharioudakis E, Menichetti S. SIRT2-selective thienopyrimidines for neurodegeneration. ACS Med Chem Lett. 2018;9(6):541–546.
[41] Actis ML, Ambrose AJ, Wright DL. Thienopyrimidines disrupting REV7 interactions. Chem Biol. 2017;24(8):1018–1025.
[42] Patel K, Shah P, Gupta R. Anti-inflammatory thienopyrimidines targeting cytokines. Eur J Pharmacol. 2019; 858:172472.
[43] Zhang J, Wang X, Li P. Thienopyrimidines as DGAT1 inhibitors for obesity and diabetes. J Med Chem. 2018;61(5):2137–2148.
[44] Gao H, Sun L, Wang Y. Inhibition of Clostridium difficile toxins by thienopyrimidines. ACS Infect Dis. 2020;6(4):643–653.
[45] Yamada M, Sato T, Ito H. Mitochondrial respiratory enzyme inhibition in Helicobacter pylori by thienopyrimidines. BiochimBiophys Acta Bioenerg. 2021;1862(2):148328.