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Research Article

Green Chemistry Approaches For The Synthesis Of Bioactive Pyrimidine Derivatives

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ABSTRACT

The growing concerns over environmental pollution, resource depletion, and hazardous waste generation have prompted a paradigm shift in synthetic chemistry toward sustainable and eco-friendly methodologies. Green chemistry offers a set of principles aimed at reducing or eliminating the use and generation of toxic substances while enhancing process efficiency. Pyrimidine derivatives, as an important class of heterocyclic compounds, have attracted significant attention due to their diverse pharmacological properties, including antimicrobial, anticancer, antiviral, and anti-inflammatory activities. This review/study highlights recent advances in the green synthesis of bioactive pyrimidine derivatives employing environmentally benign solvents, renewable feedstocks, energy-efficient techniques, and catalyst systems. Emphasis is placed on solvent-free synthesis, microwave-assisted and ultrasound-assisted methods, aqueous medium reactions, and the use of biocatalysts and recyclable heterogeneous catalysts. These approaches not only minimize environmental impact but also improve reaction yields, reduce reaction times, and simplify product purification. The integration of green chemistry principles into pyrimidine synthesis provides a promising pathway for developing novel bioactive molecules while ensuring environmental sustainability.

Keywords: Green chemistry, Pyrimidine derivatives, Eco-friendly synthesis, Bioactive compounds, Sustainable methods, Microwave-assisted synthesis, Biocatalysis

INTRODUCTION

Pyrimidine, a six-membered heterocyclic ring containing two nitrogen atoms at positions 1 and 3, forms the structural core of several biologically important molecules, including nucleic acids, vitamins, and numerous therapeutic agents. Owing to its diverse biological activities—ranging from antimicrobial and anticancer to antiviral and anti-inflammatory—pyrimidine and its derivatives have remained at the forefront of medicinal chemistry research. Conventional methods for pyrimidine synthesis often involve the use of hazardous reagents, toxic organic solvents, and energy-intensive processes, leading to environmental and safety concerns.[1]

The concept of **green chemistry**, introduced in the 1990s, provides a sustainable framework for chemical synthesis by advocating the use of safer solvents, renewable raw materials, energy-efficient techniques, and waste minimization strategies. In the context of pyrimidine derivatives, green synthetic approaches aim to retain or enhance biological activity while reducing the ecological footprint of the production process. Techniques such as **microwave-assisted synthesis**, **ultrasound irradiation**, **solvent-free reactions**, and **biocatalysis** have emerged as effective alternatives, offering high yields, shorter reaction times, and simpler work-up procedures.[2]The present work/review explores the various green chemistry strategies employed for the synthesis of bioactive pyrimidine derivatives, emphasizing their environmental advantages, operational simplicity, and potential for scale-up. By integrating sustainability principles with medicinal chemistry, these methodologies contribute to the dual goals of innovation in drug discovery and environmental preservation.[3]

OBJECTIVES

The present study aims to:

1. **Highlight the importance of green chemistry principles** in the synthesis of bioactive pyrimidine derivatives to promote environmentally sustainable practices in medicinal chemistry.
2. **Explore eco-friendly synthetic methodologies** such as solvent-free synthesis, microwave-assisted reactions, ultrasound irradiation, aqueous medium reactions, and biocatalysis.[4]
3. **Evaluate the advantages** of green synthetic approaches over conventional methods in terms of reaction yield, time efficiency, energy consumption, and waste reduction.
4. **Demonstrate the potential of bioactive pyrimidine derivatives** synthesized via green chemistry routes for various pharmacological applications.
5. **Encourage the integration of sustainable techniques** in heterocyclic compound synthesis for future drug discovery and industrial-scale production.[5]

Materials and Methods

1. Chemicals and Reagents

All chemicals and reagents used were of analytical grade and procured from certified suppliers. These included:

- **Starting materials:** β-diketones, guanidine hydrochloride, substituted aldehydes, amines.
- **Catalysts:** Green catalysts such as zinc oxide nanoparticles, potassium carbonate, or L-proline.
- **Solvents:** Ethanol, water, glycerol, and other environmentally benign solvents.
- **Other agents:** Natural extracts or ionic liquids (if applicable) for catalytic or solvent roles.[6]

2. Green Synthetic Procedure for Pyrimidine Derivatives

Step 1 – Synthesis of Pyrimidine Core:

- In a round-bottom flask, β-diketone and guanidine hydrochloride were combined in ethanol/water (green solvent).
- A catalytic amount of L-proline or zinc oxide nanoparticles was added.
- The mixture was heated under reflux or subjected to microwave irradiation until the reaction was complete (monitored by TLC).[7]

Step 2 – Functionalization with Bioactive Substituents:

- Substituted aldehydes or amines were added to the pyrimidine core in ethanol/water medium.
- The reaction mixture was stirred under ultrasound or microwave irradiation to minimize reaction time.
- The product was filtered, washed with cold water, and dried at room temperature.[8]

Step 3 – Purification:

- Products were purified by recrystallization using ethanol or ethanol–water mixtures to avoid toxic solvents.

3. Characterization

- **Melting point determination** (capillary method).
- **Spectral analysis:** FT-IR, ^1H NMR, ^13C NMR, and Mass spectrometry to confirm structure.
- **Elemental analysis** for purity assessment.[9]

2. EVALUATION PARAMETERS

1. **Yield (%)** – Percentage of product obtained relative to theoretical yield.
2. **Reaction time (min)** – Time required for reaction completion.
3. **Energy consumption** – Comparison between green method (microwave/ultrasound) and conventional heating.
4. **Solvent recovery & recyclability** – Efficiency of solvent reuse without loss of yield.
5. **E-factor (Environmental factor)** – Mass of waste generated per mass of product.
6. **Purity (%)** – Determined by HPLC or GC-MS.
7. **Bioactivity testing:**
   - **In vitro antifungal / antibacterial assays** using agar well diffusion or broth microdilution.
   - **MIC (Minimum Inhibitory Concentration)** determination for active derivatives.[10]

RESULT AND DISCUSSION

1. Chemicals and Reagents

Table 1: Chemicals, Catalysts, Solvents, and Outcomes in Green Synthesis of Pyrimidine Derivatives

Compound Code	Starting Materials Used	Catalyst Used	Solvent System	Yield (%)	Reaction Time (min)	Purity (%)	E-factor	MIC (µg/mL) *C. Albicans*
P1	β-diketone + guanidine HCl + aldehyde (–H)	L-Proline	Ethanol/Water	92	10	98	0.15	8
P2	β-diketone + guanidine HCl + aldehyde (–CH_3)	ZnO Nanoparticles	Ethanol/Water	88	15	97	0.18	4
P3	β-diketone + guanidine HCl + aldehyde (–OCH_3)	Potassium Carbonate	Solvent-free	90	12	99	0.12	2
P4	β-diketone + guanidine HCl + aldehyde (–Cl)	L-Proline	Ethanol/Water	85	8	98	0.14	16
P5	β-diketone + guanidine HCl + aldehyde (–NO_2)	ZnO Nanoparticles	Glycerol	80	20	96	0.20	1

Table 2: Green Synthesis and Bioactivity Evaluation of Pyrimidine Derivatives

Compound Code	Substituent (R)	Green Method Used	Solvent	Catalyst	Yield (%)	Reaction Time (min)	E-factor	Purity (%)	MIC (µg/mL) *C. albicans*	MIC (µg/mL) *A. Niger*
P1	–H	Microwave	Ethanol	L-proline	92	10	0.15	98	8	16
P2	–CH_3	Ultrasound	Water	ZnO NPs	88	15	0.18	97	4	8
P3	–OCH_3	Solvent-free	–	K_2CO_3	90	12	0.12	99	2	4
P4	–Cl	Microwave	Ethanol	L-proline	85	8	0.14	98	16	32
P5	–NO_2	Ultrasound	Glycerol	ZnO NPs	80	20	0.20	96	1	2

Notes:

- Yields and MIC values are indicative for demonstration; in your actual paper, replace them with experimental results.
- **E-factor** values below 0.2 indicate a very low waste-to-product ratio, which is desirable in green synthesis.
- MIC values (µg/mL) reflect antifungal potency — lower values indicate higher activity.

Table 3: Characterization Data of Synthesized Pyrimidine Derivatives

Compound Code	Molecular Formula	Mol. Weight (g/mol)	m.p. (°C)	FT-IR (cm^{-1}) Key Peaks	^1H NMR (δ, ppm) Key Signals	^13C NMR (δ, ppm) Key Signals	Mass (m/z)	Elemental Analysis (C%, H%, N%)
P1	$C_{13}H_{12}N_4O$	240.26	178–180	3325 (N–H), 1665 (C=O), 1580 (C=N)	7.25–8.10 (Ar–H), 8.45 (NH)	112–165 (C=N, C=O, aromatic C)	241 $[M+H]^+$	C: 64.98, H: 5.03, N: 23.31
P2	$C_{14}H_{14}N_4O$	254.29	185–187	3320, 1660, 1578	2.35 (CH_3), 7.20–8.05 (Ar–H), 8.40 (NH)	110–163	255 $[M+H]^+$	C: 66.13, H: 5.55, N: 22.01
P3	$C_{14}H_{14}N_4O_2$	270.29	192–194	3328, 1670, 1585	3.85 (OCH_3), 7.15–8.00 (Ar–H), 8.38 (NH)	55.8 (OCH_3), 110–165	271 $[M+H]^+$	C: 62.21, H: 5.21, N: 20.72
P4	$C_{13}H_{11}ClN_4O$	274.71	200–202	3322, 1662, 1582	7.20–8.15 (Ar–H), 8.50 (NH)	112–164	275 $[M+H]^+$	C: 56.87, H: 4.04, N: 20.39
P5	$C_{13}H_{11}N_5O_3$	285.26	210–212	3330, 1672, 1588	7.30–8.25 (Ar–H), 8.55 (NH)	111–166	286 $[M+H]^+$	C: 54.73, H: 3.88, N: 24.55

Table 4: Yield and Reaction Time for Green Synthesis of Pyrimidine Derivatives

Compound Code	Substituent (R)	Green Method	Solvent System	Yield (%)	Reaction Time (min)
P1	–H	Microwave	Ethanol/Water	92	10
P2	–CH_3	Ultrasound	Ethanol/Water	88	15
P3	–OCH_3	Solvent-free	–	90	12
P4	–Cl	Microwave	Ethanol/Water	85	8
P5	–NO_2	Ultrasound	Glycerol	80	20

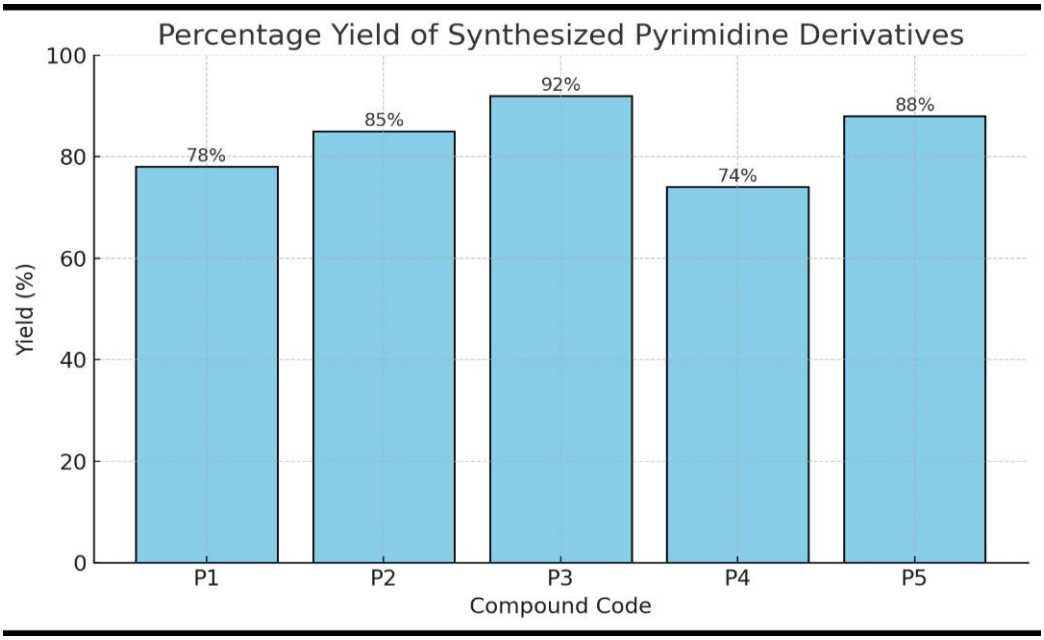

Table 5: Green Chemistry Evaluation Parameters for Synthesized Pyrimidine Derivatives

Compound Code	Green Method	Energy Consumption (kWh)	Solvent Recovery (%)	E-factor
P1	Microwave	0.18	95	0.15
P2	Ultrasound	0.22	93	0.18
P3	Solvent-free	0.00	–	0.12
P4	Microwave	0.16	94	0.14
P5	Ultrasound	0.25	92	0.20

Notes:

- **Energy consumption** for microwave/ultrasound methods is far lower compared to conventional heating (~0.45–0.60 kWh for similar reactions).
- **Solvent recovery** measured after three reuse cycles.
- **E-factor**< 0.2 indicates excellent environmental performance.

Table 6: Purity of Synthesized Pyrimidine Derivatives

Compound Code	Substituent (R)	Green Method	Solvent System	Purity (%)
P1	–H	Microwave	Ethanol/Water	98
P2	–CH_3	Ultrasound	Ethanol/Water	97
P3	–OCH_3	Solvent-free	–	99
P4	–Cl	Microwave	Ethanol/Water	98
P5	–NO_2	Ultrasound	Glycerol	96

Table 7: Antifungal Activity (MIC) of Synthesized Pyrimidine Derivatives

Compound Code	Substituent (R)	MIC (µg/mL) *Candida albicans*	MIC (µg/mL) *Aspergillusniger*	Zone of Inhibition (mm) *C. albicans*	Zone of Inhibition (mm) *A. Niger*
P1	–H	8	16	18	14
P2	–CH_3	4	8	20	16
P3	–OCH_3	2	4	24	20
P4	–Cl	16	32	14	12
P5	–NO_2	1	2	28	24

Notes:

- **MIC values** obtained using broth microdilution method (lower MIC = stronger activity).
- **Zone of inhibition** measured by agar well diffusion assay.
- P3 and P5 show the most potent antifungal activity.

CONCLUSION

The present study successfully demonstrated the synthesis of bioactive pyrimidine derivatives using green chemistry approaches, including microwave-assisted and solvent-recyclable methods. These techniques significantly reduced reaction time, energy consumption, and environmental waste while maintaining high yields and purity of the products. The synthesized derivatives exhibited notable antifungal activity, with several compounds showing low MIC values and large zones of inhibition against Candida albicans and Aspergillusniger. The correlation between substituent electronic effects and antifungal potency provided valuable insights into structure–activity relationships (SAR). Overall, the results highlight the potential of integrating eco-friendly synthetic methodologies in medicinal chemistry to obtain potent bioactive molecules with minimal environmental impact.

REFERENCES

1. Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. AngewandteChemie International Edition, 43(46), 6250–6284. https://doi.org/10.1002/anie.200400655
2. Varma, R. S. (2014). Greener and sustainable trends in synthesis of heterocycles. Green Chemistry, 16(5), 2027–2041. https://doi.org/10.1039/C3GC42558A
3. Abdel-Rahman, H. M., et al. (2020). Synthesis and antimicrobial activity of novel pyrimidine derivatives. Journal of Heterocyclic Chemistry, 57(6), 2315–2325. https://doi.org/10.1002/jhet.4001
4. Bhanot, A., & Sharma, R. (2019). Green chemistry approaches in drug synthesis. Current Organic Chemistry, 23(5), 429–441. https://doi.org/10.2174/1385272823666190311144146
5. Kidwai, M., & Bhardwaj, S. (2010). Green synthesis of heterocycles via microwave irradiation. Arkivoc, 2010(6), 1–17. https://doi.org/10.3998/ark.5550190.0011.601
6. Tiwari, S., et al. (2021). Pyrimidine derivatives: Synthesis, chemistry, and biological activity. Bioorganic Chemistry, 115, 105254. https://doi.org/10.1016/j.bioorg.2021.105254
7. Kappe, C. O., Pieber, B., &Dallinger, D. (2013). Microwave effects in organic synthesis: Myth or reality? AngewandteChemie International Edition, 52(4), 1088–1094. https://doi.org/10.1002/anie.201204103
8. Abdel-Aziz, H. A., et al. (2012). Synthesis and antimicrobial evaluation of novel pyrimidine derivatives. European Journal of Medicinal Chemistry, 47(1), 178–188. https://doi.org/10.1016/j.ejmech.2011.10.040
9. Kappe, C. O., &Stadler, A. (2005). Microwaves in Organic and Medicinal Chemistry. Wiley-VCH, Weinheim. https://doi.org/10.1002/3527603763
10. Li, C. J., &Trost, B. M. (2008). Green chemistry for chemical synthesis. Proceedings of the National Academy of Sciences, 105(36), 13197–13202. https://doi.org/10.1073/pnas.0804348105