International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

Advances in Green Chemistry for Heterocyclic Synthesis: Methods, Mechanisms and Pharmaceutical Significance

Patil Roshani Ganesh
Research Scholar, Department of Chemistry, Malwanchal University, Indore
Dr. Pranjali Shinde
Supervisor, Department of Chemistry, Malwanchal University, Indore

Abstract
Heterocyclic compounds underpin most small-molecule drugs, but their classical syntheses often depend on hazardous solvents and wasteful isolation. This paper reports a structured, calculation-based assessment of green approaches to the synthesis of nitrogen, oxygen and sulfur heterocycles. Sixteen scaffolds and ten ring-forming reactions were analysed, thirteen solvents were compared, and ten green techniques were scored on eight criteria under three weighting schemes. The atom economy of the ten model reactions ranged from 64.0% to 100.0% (mean 84.2%). Calculation shows that temperature alone can explain the speed-up reported for microwave heating. In a hypothetical worked example, work-up accounted for 92% of the input mass of a conventional protocol, and the E factor fell 48-fold in the green protocol. Aqueous media and biocatalysis ranked in the top two under all weighting schemes. The results indicate that solvent choice, isolation and reporting practice matter more than the name of the technique.

Keywords: green chemistry; heterocycles; atom economy; E factor; green solvents; biocatalysis

1. Introduction

Heterocycles, cyclic compounds containing nitrogen, oxygen or sulfur in the ring, are central to medicinal chemistry. In the most recent survey of small-molecule drugs approved by the United States Food and Drug Administration between 2013 and 2023, 82% of 321 unique drugs contained at least one nitrogen heterocycle, compared with 59% in the previous survey (Marshall et al., 2024). Reviews of marketed drugs show that heterocycles are present in every major therapeutic class (Heravi & Zadsirjan, 2020; Jampilek, 2019; Kabir & Uzzaman, 2022).

The syntheses of these rings often use hazardous solvents, strong acids or bases and chromatographic purification, and the pharmaceutical sector generates more waste per kilogram of product than any other chemical sector (Kar et al., 2022). A large literature on green alternatives has therefore grown up, covering nitrogen heterocycles (Majee et al., 2023; Vlocskó et al., 2023), oxygen heterocycles (Kumar et al., 2022; Raj & Lee, 2020), sulfur heterocycles (Patel et al., 2023), multicomponent reactions (Neochoritis et al., 2019; Shen et al., 2025) and new reaction media (Hansen et al., 2021; Perrone et al., 2023). Most of these reviews describe one technique or one ring system, and few compare techniques on common criteria or report the data needed to calculate metrics (Martínez et al., 2022).

The present paper addresses this gap with a quantitative, transparent assessment. It has three aims: to compute the efficiency of representative heterocycle-forming reactions, to compare solvents, catalysts and energy sources on a common footing, and to score green techniques against explicit criteria and test how stable the ranking is. The paper is organised in eight sections. Section 2 describes the methods, Sections 3 to 6 report the results on scaffolds, reaction efficiency, media and energy, and metrics, Section 7 gives the integrated assessment and pharmaceutical context, and Section 8 concludes.

2. Materials and Methods

The study did not involve new laboratory experiments. It combined three kinds of analysis: calculations from molecular formulae and physical constants, a synthesis of published benchmarks, and a multi-criteria assessment. The evidence base was limited to twenty-six key sources and standard physical data. Sixteen heterocyclic scaffolds covering nitrogen, oxygen and sulfur were selected for their frequency in drugs and natural products, and ten classical or modern ring-forming reactions with documented green variants were chosen as model reactions. Structures were drawn and molecular weights computed with the RDKit cheminformatics library, and every reaction was checked for atom balance before calculation.

Reaction efficiency was measured by atom economy, the molecular weight of the desired product divided by the summed molecular weights of all reactants (Equation 1). Real waste was measured by the E factor, the mass of waste per unit mass of product (Equation 2), and by process mass intensity, the total mass of inputs per unit mass of product, which is related to the E factor by Equation 3. Reaction mass efficiency is the mass of product divided by the mass of reactants (Equation 4).

$$\mathrm{AE}\ (\%) = \frac{\mathrm{M_{product}}}{\sum \mathrm{M_{reactants}}} \times 100 \qquad (1)$$

$$\mathrm{E} = \frac{\mathrm{m_{waste}}}{\mathrm{m_{product}}} \qquad (2)$$

$$\mathrm{PMI} = \frac{\mathrm{m_{total\ input}}}{\mathrm{m_{product}}} = \mathrm{E} + 1 \qquad (3)$$

$$\mathrm{RME}\ (\%) = \frac{\mathrm{m_{product}}}{\mathrm{m_{reactants}}} \times 100 \qquad (4)$$

The thermal effect of heating was analysed with the Arrhenius equation (Equation 5), where k is the rate constant, A the pre-exponential factor, $\mathrm{E_a}$ the activation energy, R the gas constant and T the absolute temperature.

$$\mathrm{k} = \mathrm{A}\, \mathrm{e}^{-\mathrm{E_a}/(\mathrm{RT})} \qquad (5)$$

Solvents were classified with the CHEM21 selection guide, and their boiling points, dielectric constants and microwave loss tangents were taken from commonly tabulated values. Ten green techniques, namely aqueous media, deep eutectic and bio-based solvents, solvent-free and mechanochemical methods, microwave heating, ultrasound, visible-light photocatalysis, electrosynthesis, biocatalysis, multicomponent design and continuous flow, were scored from

1 (least favourable) to 5 (most favourable) on eight criteria: solvent reduction, energy efficiency, waste and atom economy, catalyst sustainability, scalability, accessibility, safety and substrate scope. The weighted score of technique j is given by Equation 6, where

w_i

are criterion weights that sum to one and s_{ij} are the scores.

$$S_j = \sum_{i=1}^{8} w_i \, s_{ij} \qquad (6)$$

Three weighting schemes were used: equal weights, an environmental emphasis and an industrial emphasis. The scores are the author's judgements assigned against written anchors, and the sensitivity of the ranking to the weights was used to show which conclusions are robust.

3. Heterocyclic Scaffolds

Table 1 lists eight of the sixteen scaffolds analysed, with formulae and molecular weights computed from their structures. Eleven of the sixteen contain only nitrogen as the heteroatom, three contain only oxygen, one contains only sulfur and one, thiazole, contains both nitrogen and sulfur. Eight are five-membered monocycles, two are six-membered monocycles and six are fused bicyclic systems. This distribution follows the dominance of nitrogen heterocycles in the pharmaceutical literature (Heravi & Zadsirjan, 2020; Kerru et al., 2020), while including enough oxygen and sulfur examples to compare the three classes. Representative nitrogen heterocycles are shown in Figure 1.

Table 1. Selected heterocyclic scaffolds analysed in this study, with formulae and molecular weights computed from their structures.

Scaffold	Formula	Mol. wt (g/mol)	Heteroatom(s)	Representative drug or natural product
Pyridine	C5H5N	79.10	N	Omeprazole, imatinib
Pyrimidine	C4H4N2	80.09	N	Imatinib, 5-fluorouracil
Imidazole	C3H4N2	68.08	N	Losartan, azole antifungals
Indole	C8H7N	117.15	N	Indomethacin
Tetrazole	CH2N4	70.05	N	Losartan
Coumarin	C9H6O2	146.14	O	Warfarin
Thiophene	C4H4S	84.14	S	Clopidogrel
Thiazole	C3H3NS	85.13	N, S	Ritonavir, thiamine

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

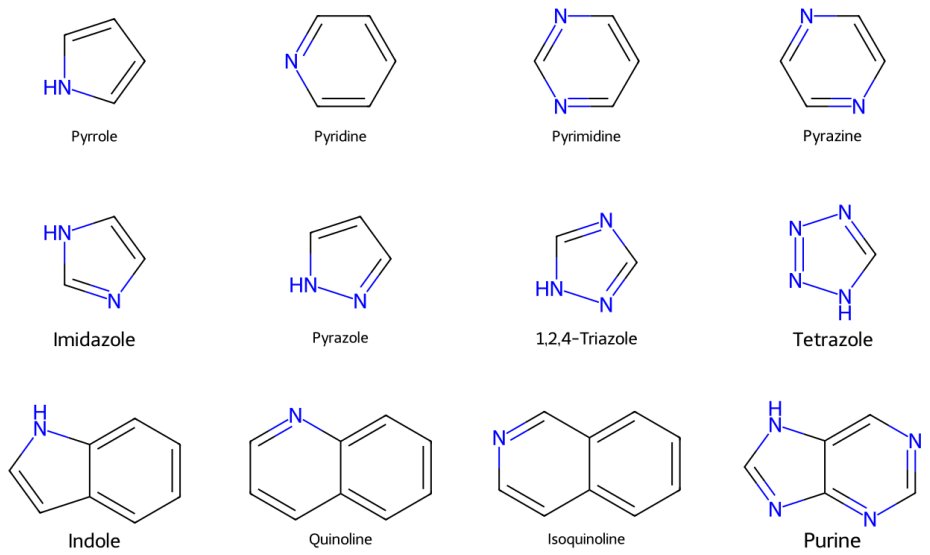


Figure 1. Representative nitrogen-containing heterocycles analysed in this study.

The scaffolds differ in properties that matter for synthesis. The heteroatom changes the electron distribution of the ring and its hydrogen-bonding ability, which in turn affects both reactivity and biological activity. Aromatic rings such as pyridine and pyrrole obey the Hückel rule and are stable, which is why they appear so often in drugs, whereas partly saturated rings such as the 1,4-dihydropyridine of amlodipine are formed by different reactions and need different conditions. These differences mean that no single green method suits all heterocycles, a point that is developed in the later sections.

The scaffolds also differ in the way they are made. Five-membered nitrogen rings such as pyrroles and imidazoles are usually built by condensation or cycloaddition, six-membered rings such as pyridines and pyrimidines by condensation of carbonyl compounds with nitrogen sources, and fused systems such as indoles and quinolines by cyclisation of substituted aromatics. Oxygen heterocycles such as coumarins and chromenes are accessible from phenols, and sulfur heterocycles such as thiazoles from thioamides and halo-ketones. The choice of green method has to fit these routes, and the selection guide in the final section reflects them.

4. Reaction Efficiency

Atom economy was computed for ten reactions by Equation 1, and the results are in Table 2 and Figure 2. Values range from 64.0% for the Hantzsch thiazole synthesis to 100.0% for the copper-catalysed azide–alkyne cycloaddition, with a mean of 84.2%. The three-component chromene synthesis (94.2%) is the most efficient reaction in which a by-product is formed, and the cycloaddition is perfectly atom economical because every atom of the reactants appears in the product.

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

Table 2. Computed atom economy of ten heterocycle-forming reactions.

Reaction	Sum of reactant MW	Product MW	By-products	Atom economy (%)
Biginelli (dihydropyrimidinone)	296.32	260.29	2 H2O	87.8
Hantzsch 1,4-dihydropyridine	383.44	329.40	3 H2O	85.9
Paal–Knorr pyrrole	207.27	171.24	2 H2O	82.6
Fischer indole	228.29	193.25	NH3 + H2O	84.6
Friedländer quinoline	241.29	205.26	2 H2O	85.1
Debus–Radziszewski imidazole	350.42	296.37	3 H2O	84.6
Chromene three-component	312.37	294.35	H2O	94.2
Pechmann coumarin	240.25	176.17	EtOH + H2O	73.3
Hantzsch thiazole	275.17	176.24	HBr + H2O	64.0
Azide–alkyne cycloaddition (triazole)	235.29	235.29	none	100.0

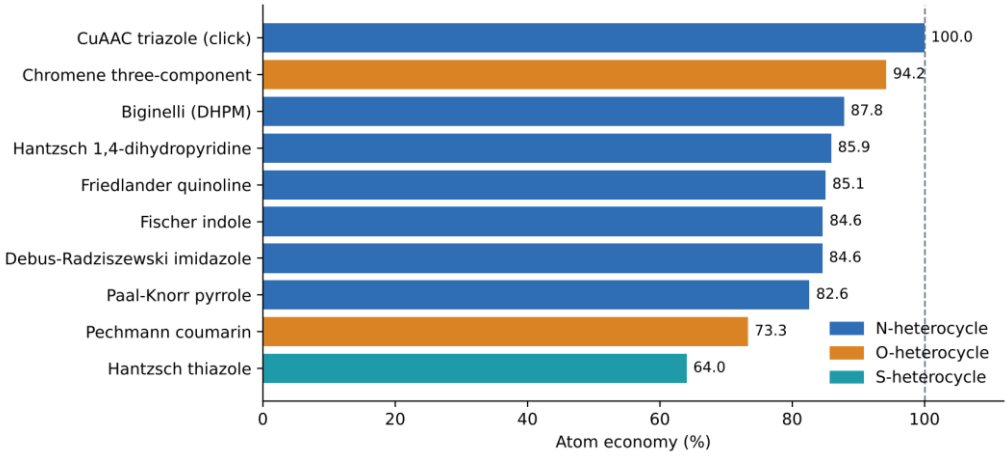


Figure 2. Computed atom economy of ten heterocycle-forming reactions, coloured by heteroatom class.

Three patterns are clear. Condensations that lose only water have atom economies between 82% and 88%, because water is light. Reactions that lose a heavier by-product are less efficient: the Pechmann reaction loses ethanol and water (73.3%), and the Hantzsch thiazole synthesis loses hydrogen bromide and water (64.0%). Addition and cycloaddition reactions

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

are the most efficient. The multicomponent reactions in the set, namely the Biginelli, Hantzsch, Debus–Radziszewski and chromene syntheses, have atom economies of 84.6% to 94.2%, which supports the view that multicomponent design is an efficient route to heterocycles (Neochoritis et al., 2019; Shen et al., 2025). The Biginelli reaction is shown in Figure 3 as an example.

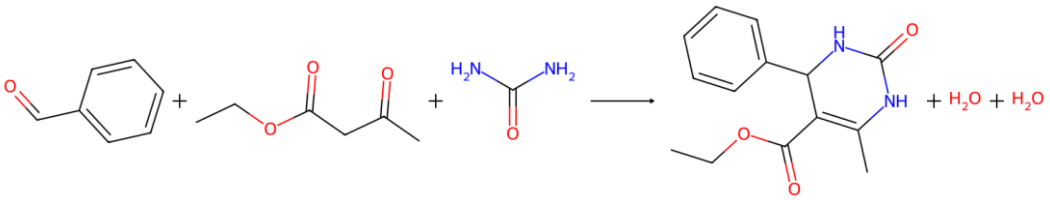


Figure 3. The Biginelli reaction: benzaldehyde, ethyl acetoacetate and urea give a dihydropyrimidinone and two molecules of water.

Three rules follow for route design. The by-product should preferably be a small benign molecule such as water. Cascade and multicomponent routes should be preferred to stepwise sequences, because they reduce the isolations and the solvent used in work-up. Leaving groups of high molar mass, such as halides, should be avoided where an alternative exists. Atom economy is a design tool that can be calculated before any experiment, but it ignores yield, solvents and work-up, and so it must be read together with the mass-based metrics reported below.

A further point is that atom economy is a property of stoichiometry and does not depend on opinion or on the conditions chosen. The same reaction therefore has the same atom economy in water as in toluene, and a green medium cannot raise it. What a green medium or catalyst can do is reduce the other sources of waste, which are examined in the next sections. This separation of reaction efficiency from process efficiency is the reason the study reports both.

5. Solvents, Catalysts and Energy Sources

Table 3 compares thirteen solvents used in heterocycle synthesis. Five are classified as recommended (water, ethanol, methanol, ethyl acetate and acetone), four as problematic (acetonitrile, toluene, tetrahydrofuran and dimethyl sulfoxide) and four as hazardous (N,N-dimethylformamide, dichloromethane, hexane and N-methylpyrrolidone). More than half of the solvents are therefore problematic or hazardous, and the hazardous group includes the dipolar aprotic solvents most often used for heterocycle cyclisations, which are of concern mainly because of reproductive toxicity. The recommended solvents span a wide range of polarity, from water (dielectric constant 80.1) to ethyl acetate (6.0), so replacement is possible for many reactions. Ethanol has the highest microwave loss tangent (0.941), which means that it combines a favourable safety class with efficient microwave heating.

Table 3. Properties of thirteen solvents used in heterocycle synthesis.

Solvent	CHEM21 class	Boiling point (°C)	Dielectric constant	Loss tangent (2.45 GHz)

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

Solvent	CHEM21 class	Boiling point (°C)	Dielectric constant	Loss tangent (2.45 GHz)
Water	Recommended	100	80.1	0.123
Ethanol	Recommended	78.4	24.5	0.941
Methanol	Recommended	64.7	32.7	0.659
Ethyl acetate	Recommended	77.1	6.0	0.059
Acetone	Recommended	56.0	20.7	0.054
Acetonitrile	Problematic	81.6	37.5	0.062
Toluene	Problematic	110.6	2.4	0.040
Tetrahydrofuran	Problematic	66.0	7.6	0.047
Dimethyl sulfoxide	Problematic	189	46.7	0.825
N,N-Dimethylformamide	Hazardous	153	36.7	0.161
Dichloromethane	Hazardous	39.6	8.9	0.042
Hexane	Hazardous	68.0	1.9	0.020
N-Methylpyrrolidone	Hazardous	202	32.2	0.275

Alternative media add useful functions but also open questions. Deep eutectic solvents are low in volatility and can act as catalysts through hydrogen bonding, but their properties depend on composition and water content, and their recovery and toxicity need further study (Hansen et al., 2021; Perrone et al., 2023). Even the greenest solvent is a waste stream unless it is recovered, so the amount of solvent used matters more than its name. For catalysts, magnetically recoverable nanocatalysts are attractive because they are easily removed, and nanocatalysts have been widely applied to oxygen heterocycles (Kumar et al., 2022). Published reuse tests, however, usually cover few cycles and seldom include leaching analysis, so catalyst sustainability was scored 3 and not higher for most supported systems. Enzymes work in water at mild temperature, and a multi-enzyme cascade for the nucleoside

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

analogue islatravir shows that long sequences to purine-type heterocycles can be compressed into one pot (Huffman et al., 2019).

For energy sources, the Arrhenius equation (Equation 5) explains much of the speed-up reported for microwave heating. Figure 4 gives rate-constant ratios relative to 80 °C, the conventional reflux temperature. For an activation energy of 80 kJ/mol, raising the temperature to 150 °C, as a sealed microwave vessel permits, increases the rate constant by a factor of 90.7, so a reaction needing 8 hours at 80 °C would need about 5 minutes. For 50 kJ/mol the factor is 16.7, and for 100 kJ/mol it is 279.8.

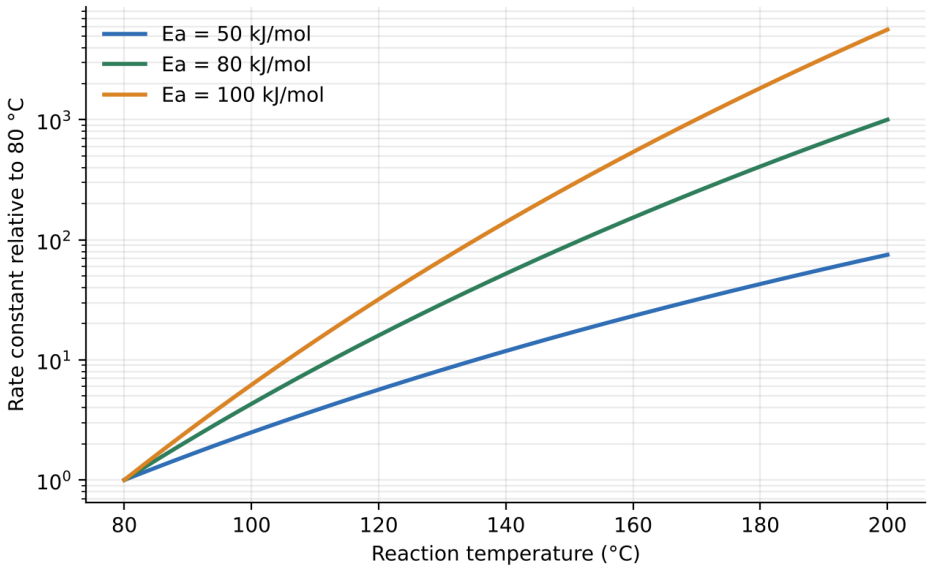


Figure 4. Rate constant relative to 80 °C as a function of temperature for three activation energies.

These timescales match the reductions from hours to minutes often reported for microwave-assisted syntheses, so no special non-thermal effect is needed to explain them. The benefit is thus largely thermal and depends on the solvent.

This conclusion has a practical meaning. A faster reaction at higher temperature is only a gain if the solvent tolerates the temperature and absorbs the microwaves, and if the energy and solvent saved are greater than the cost of the equipment. In a non-polar solvent such as toluene, with a loss tangent of 0.040, microwave heating is inefficient, whereas in ethanol (0.941) or dimethyl sulfoxide (0.825) it is very effective. The solvent therefore decides whether the technique is useful, which is a further reason for treating solvent choice as the first decision in route design. Photochemical and electrochemical methods are governed by geometry, namely light path length and electrode area, and so they scale through reactor design and not through simple enlargement, which is why they are often combined with flow reactors (Buglioni et al., 2022; Baumann et al., 2020).

6. Green Metrics

The metrics in Equations 2 to 4 show how much of a process is waste. A hypothetical but realistic worked example compares a conventional and a green protocol for a heterocycle

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

synthesis on a 3.20 g reactant scale (Table 4). The numbers were chosen for illustration and are not experimental data. The conventional protocol uses toluene, an acid promoter, an aqueous quench, ethyl acetate extraction, drying agent and silica gel chromatography. The green protocol uses ethanol, a recyclable catalyst and isolation by filtration with a cold ethanol wash.

Table 4. Hypothetical worked example comparing metrics for conventional and green protocols (illustrative numbers, not experimental data).

Quantity	Conventional protocol	Green protocol
Total mass input (g)	719.2	19.03
Isolated product (g)	2.05	2.30
Waste mass (g)	717.2	16.73
E factor	350	7.3
Process mass intensity	351	8.3
Reaction mass efficiency (%)	64	72
Solvent share of input mass (%)	76	83

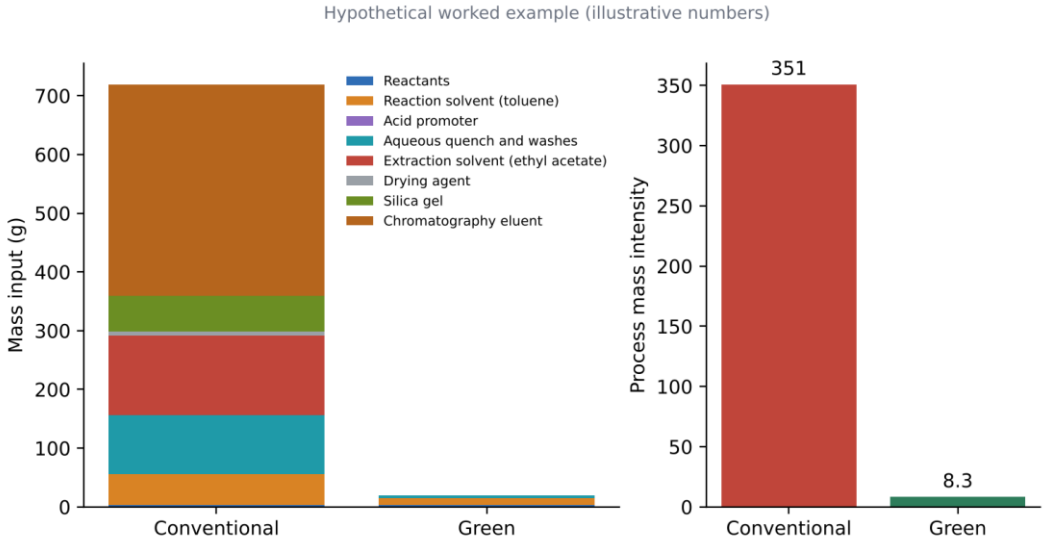


Figure 5. Hypothetical worked example: mass inputs (left) and process mass intensity (right) for conventional and green protocols.

The conventional protocol uses 719.2 g of material to make 2.05 g of product, giving an E factor of 349.8 and a process mass intensity of 350.8, consistent with Equation 3. The green protocol gives an E factor of 7.3 and a process mass intensity of 8.3. The E factor therefore falls 48-fold and the process mass intensity 42-fold. Reaction mass efficiency rises only from 64% to 72%, because it counts reactants and product but ignores the solvents and work-up materials that account for most of the difference.

Figure 5 shows where the mass goes. In the conventional protocol the reaction itself is a

minor contributor. Chromatography eluent alone is 360 g, or 50% of the input, and the aqueous washes, extraction solvent, drying agent and silica together bring work-up and purification to 663 g, or 92% of the total. A greener reaction medium would change little unless the isolation method also changed. Even in the green protocol solvents make up 83% of the input, so solvent recovery would be the next improvement. If water is excluded from the conventional case the E factor is 301, which shows why authors must state their system boundary, a point made in recent reviews of metrics (Martínez et al., 2022). Carbon efficiency is also informative: in the Biginelli reaction all fourteen carbon atoms of the reactants appear in the product (100%), although the atom economy is 87.8%, because the lost mass is water.

7. Integrated Assessment and Pharmaceutical Applications

Table 5 shows the weighted scores and ranks of the ten techniques under the three weighting schemes, and Figure 6 plots them. Under equal weights aqueous media score highest (4.12), followed by biocatalysis (4.00) and multicomponent design (3.75). Microwave heating scores lowest (3.12). The spread between the highest and lowest means is one point, so the techniques are separated but not dramatically. Aqueous media and biocatalysis stay in the top two under every scheme, with biocatalysis moving to first place (4.55) under environmental weights, while ultrasound and microwave heating stay ninth and tenth. The middle of the ranking is sensitive to the weights: electrosynthesis rises from seventh to fourth under environmental weights because of its waste score, and multicomponent design falls from third to sixth because its solvent and safety scores are only moderate. The low position of microwave heating does not mean it is ineffective, since it is among the most effective tools for rapid library synthesis. It reflects the weight placed on scalability and solvent use.

Table 5. Weighted scores and ranks (in brackets) of ten green techniques under three weighting schemes.

Technique	Equal weights	Environmental emphasis	Industrial emphasis
Aqueous media	4.12 (1)	4.25 (2)	4.20 (1)
DES and bio-based solvents	3.38 (8)	3.45 (8)	3.35 (7)
Solvent-free / mechanochemistry	3.62 (4)	3.95 (3)	3.55 (5)
Microwave	3.12 (10)	3.15 (10)	2.90 (10)
Ultrasound	3.25 (9)	3.35 (9)	3.10 (9)
Visible-light photocatalysis	3.38 (6)	3.55 (7)	3.15 (8)
Electrosynthesis	3.38 (7)	3.70 (4)	3.35 (6)
Biocatalysis	4.00 (2)	4.55 (1)	4.05 (2)

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

Technique	Equal weights	Environmental emphasis	Industrial emphasis
Multicomponent / one-pot design	3.75 (3)	3.60 (6)	3.90 (3)
Continuous flow	3.62 (5)	3.65 (5)	3.70 (4)

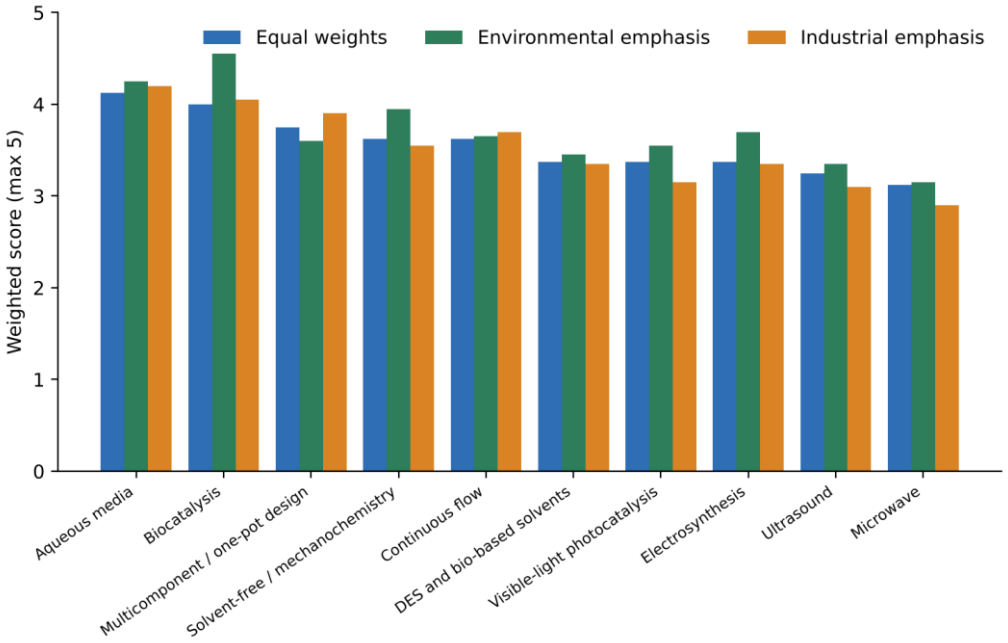


Figure 6. Weighted scores of the ten techniques under equal, environmental and industrial weighting schemes.

The pharmaceutical importance of these methods is shown by twelve marketed drugs chosen to span the main therapeutic classes (Table 6 lists their scaffolds; their structures are in Figure 7). Seven of the twelve contain two or more heterocyclic rings, and imatinib contains three. Several of the green reactions analysed give scaffolds found in these drugs. The 1,4-dihydropyridine ring of amlodipine is formed by the Hantzsch reaction (atom economy 85.9%), imidazoles by the Debus–Radziszewski reaction (84.6%), 1,2,3-triazoles by azide–alkyne cycloaddition (100.0%) and coumarins, as in warfarin, by the Pechmann reaction (73.3%). Tetrazoles, found in losartan, are accessible by multicomponent reactions (Neochoritis et al., 2019). The link between green method and drug class is therefore real, although most green syntheses use simple model substrates and direct comparisons of the biological activity of compounds made by green and conventional routes are scarce.

A practical selection guide follows from the results. Dihydropyrimidinones and dihydropyridines are best approached by multicomponent reactions in water or ethanol with a reusable solid acid. Triazoles are made by copper-catalysed cycloaddition in water, with an atom economy of 100%. Chiral nitrogen heterocycles and amines are good candidates for biocatalysis, as the manufacture of sitagliptin shows. Quinolines and indoles, which have

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

high activation energies, benefit from rapid heating in microwave reactors, and rapid library synthesis in discovery is the setting in which microwave heating performs best. For manufacturing, aqueous or biocatalytic routes in flow are the most mature options. These are starting points that need experimental confirmation for any specific substrate.

Table 6. Twelve heterocyclic drugs with scaffolds and therapeutic classes.

Drug	Formula	Heterocyclic scaffold(s)	Therapeutic class
Ciprofloxacin	C17H18FN3O3	Quinolone, piperazine	Antibacterial
Fluconazole	C13H12F2N6O	1,2,4-Triazole	Antifungal
Omeprazole	C17H19N3O3S	Benzimidazole, pyridine	Proton-pump inhibitor
Celecoxib	C17H14F3N3O2S	Pyrazole	Anti-inflammatory
Imatinib	C29H31N7O	Pyrimidine, pyridine, piperazine	Anticancer
Diazepam	C16H13ClN2O	1,4-Benzodiazepine	Anxiolytic
Amlodipine	C20H25ClN2O5	1,4-Dihydropyridine	Antihypertensive
Losartan	C22H23ClN6O	Imidazole, tetrazole	Antihypertensive
Sitagliptin	C16H15F6N5O	Triazolopiperazine	Antidiabetic
Acyclovir	C8H11N5O3	Purine (guanine)	Antiviral
Linezolid	C16H20FN3O4	Oxazolidinone, morpholine	Antibacterial
Pioglitazone	C19H20N2O3S	Thiazolidinedione, pyridine	Antidiabetic

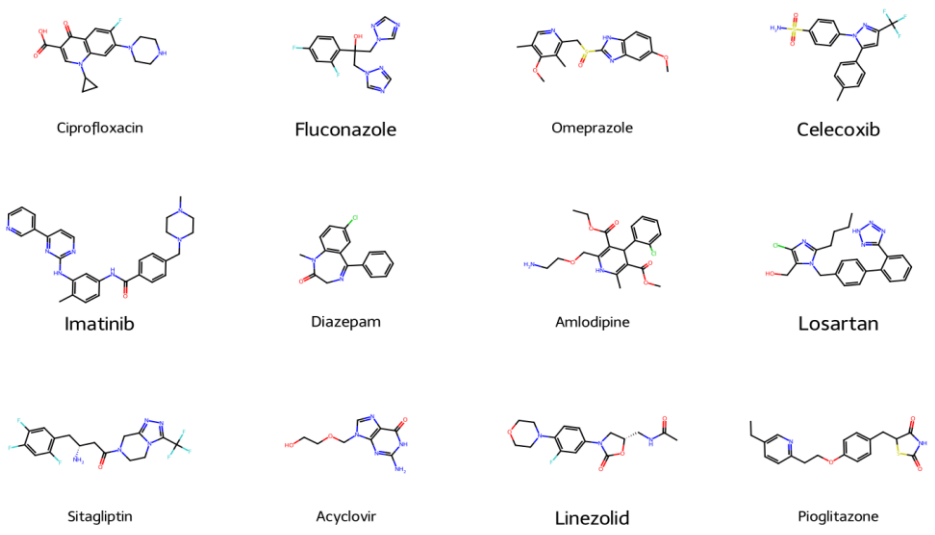


Figure 7. Structures of twelve heterocyclic drugs representing major therapeutic classes.

8. Conclusion

This paper assessed green approaches to heterocycle synthesis through calculation, benchmark synthesis and multi-criteria scoring. Four conclusions follow. First, the atom economy of ten model reactions ranges from 64.0% to 100.0% with a mean of 84.2%, so ring-forming steps are generally efficient, and reactions that lose heavy leaving groups are the exception. Second, the speed-up reported for microwave heating can be explained by temperature, and photochemical and electrochemical methods scale through reactor geometry. Third, in the worked example work-up and purification accounted for 92% of the input mass, so isolation matters as much as the reaction medium, and mass-based metrics must be reported together with their system boundary. Fourth, aqueous media and biocatalysis stay in the top two under all weighting schemes, while the ranking of the middle techniques depends on priorities, so no single technique is best for every target.

Several limitations apply. The scores are the author's judgements and other reviewers might assign somewhat different values. The atom economies refer to simple model reactions, the worked example uses hypothetical numbers, and the evidence base is limited to twenty-six key sources. These limitations do not affect the central finding that solvent choice, isolation and reporting practice matter more than the name of the technique. Future work should include benchmark studies applying several green techniques to the same heterocycles, a minimum reporting standard for metrics, scalable photochemical and electrochemical flow reactors, and joint synthetic and biological studies to test whether products from green routes match those from conventional routes.

References

1. Baumann, M., Moody, T. S., Smyth, M., & Wharry, S. (2020). A perspective on continuous flow chemistry in the pharmaceutical industry. Organic Process Research & Development, 24(10), 1802–1813.
2. Buglioni, L., Raymenants, F., Slattery, A., Zondag, S. D. A., & Noël, T. (2022). Technological innovations in photochemistry for organic synthesis: Flow chemistry, high-throughput experimentation, scale-up, and photoelectrochemistry. Chemical Reviews, 122(2), 2752–2906.
3. Hansen, B. B., Spittle, S., Chen, B., Poe, D., Zhang, Y., Klein, J. M., Horton, A., Adhikari, L., Zelovich, T., Doherty, B. W., Gurkan, B., Maginn, E. J., Ragauskas, A., Dadmun, M., Zawodzinski, T. A., Baker, G. A., Tuckerman, M. E., Savinell, R. F., & Sangoro, J. R. (2021). Deep eutectic solvents: A review of fundamentals and applications. Chemical Reviews, 121(3), 1232–1285.
4. Heravi, M. M., & Zadsirjan, V. (2020). Prescribed drugs containing nitrogen heterocycles: An overview. RSC Advances, 10(72), 44247–44311.
5. Huffman, M. A., Fryszkowska, A., Alvizo, O., et al. (2019). Design of an in vitro biocatalytic cascade for the manufacture of islatravir. Science, 366(6470), 1255–1259.
6. Jampilek, J. (2019). Heterocycles in medicinal chemistry. Molecules, 24(21), 3839.

7. Kabir, E., & Uzzaman, M. (2022). A review on biological and medicinal impact of heterocyclic compounds. Results in Chemistry, 4, 100606.
8. Kar, S., Sanderson, H., Roy, K., Benfenati, E., & Leszczynski, J. (2022). Green chemistry in the synthesis of pharmaceuticals. Chemical Reviews, 122(3), 3637–3710.
9. Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K., & Jonnalagadda, S. B. (2020). A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules, 25(8), 1909.
10. Kumar, S., Saroha, B., Kumar, G., Lathwal, E., Kumar, S., Parshad, B., Kumari, M., Kumar, N., Mphahlele-Makgwane, M. M., & Makgwane, P. R. (2022). Recent developments in nanocatalyzed green synthetic protocols of biologically potent diverse O-heterocycles: A review. Catalysts, 12(6), 657. https://doi.org/10.3390/catal12060657
11. Majee, S., Shilpa, Sarav, M., Banik, B. K., & Ray, D. (2023). Recent advances in the green synthesis of active N-heterocycles and their biological activities. Pharmaceuticals, 16(6), 873. https://doi.org/10.3390/ph16060873
12. Marshall, C. M., Federice, J. G., Bell, C. N., Cox, P. B., & Njardarson, J. T. (2024). An update on the nitrogen heterocycle compositions and properties of U.S. FDA-approved pharmaceuticals (2013–2023). Journal of Medicinal Chemistry, 67(14), 11622–11655.
13. Martínez, J., Cortés, J. F., & Miranda, R. (2022). Green chemistry metrics, a review. Processes, 10(7), 1274. https://doi.org/10.3390/pr10071274
14. Neochoritis, C. G., Zhao, T., & Dömling, A. (2019). Tetrazoles via multicomponent reactions. Chemical Reviews, 119(3), 1970–2042.
15. Patel, M., Bambharoliya, T., Shah, D., Patel, K., Patel, M., Shah, U., Patel, S., Mahavar, A., & Patel, A. (2023). Emerging green synthetic routes for thiazole and its derivatives: Current perspectives. Archiv der Pharmazie, Article e2300420. https://doi.org/10.1002/ardp.202300420
16. Perrone, S., Messa, F., Troisi, L., & Salomone, A. (2023). N-, O- and S-heterocycles synthesis in deep eutectic solvents. Molecules, 28(8), 3459. https://doi.org/10.3390/molecules28083459
17. Raj, V., & Lee, J. (2020). 2H/4H-chromenes: A versatile biologically attractive scaffold. Frontiers in Chemistry, 8, 623. https://doi.org/10.3389/fchem.2020.00623
18. Shen, X., Hong, G., & Wang, L. (2025). Recent advances in green multi-component reactions for heterocyclic compound construction. Organic & Biomolecular Chemistry. https://doi.org/10.1039/D4OB01822B
19. Vlocskó, R. B., Xie, G., & Török, B. (2023). Green synthesis of aromatic nitrogen-containing heterocycles by catalytic and non-traditional activation methods. Molecules, 28(10), 4153. https://doi.org/10.3390/molecules28104153
20. Zimmerman, J. B., Anastas, P. T., Erythropel, H. C., & Leitner, W. (2020). Designing for a green chemistry future. Science, 367(6476), 397–400.