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Synthesis of Bioactive Organic Compounds Using Green and Environmentally Friendly Catalysts

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تحضير مركبات عضوية نشطة حيويًا باستخدام محفزات خضراء وصديقة للبيئة

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Abstract

This research investigates the synthesis of bioactive organic compounds through the application of green and environmentally friendly catalysts, addressing the growing need for sustainable alternatives to conventional synthetic methods. The study encompasses a comprehensive framework for developing catalytic routes that minimize environmental impact while maintaining or improving synthetic efficiency. Biocatalysts including enzymes and whole-cell systems, metal-free organocatalysts, heterogeneous recyclable catalysts, and nanocatalysts derived from renewable sources are evaluated in terms of their ability to facilitate the synthesis of pharmacologically relevant compounds including heterocycles, alkaloids, chalcones, and coumarin-fused scaffolds. Reaction conditions are optimized with respect to catalyst loading, solvent selection emphasizing green media such as deep eutectic solvents, water, and Cyrene, temperature, and reaction time. Green chemistry metrics including atom economy, E-factor, reaction mass efficiency, turnover number (TON), and turnover frequency (TOF) are employed to quantitatively assess the environmental sustainability of the developed protocols. Results demonstrate that green catalytic systems achieve yields and selectivities comparable to or exceeding those of conventional methods, while significantly reducing waste generation and toxicity. Recyclable heterogeneous catalysts, including chitosan-based magnetic nanocomposites, biogenic metal nanocatalysts, and ash-derived reagents, demonstrate robust reusability over multiple reaction cycles. The findings underscore the

viability of integrating green chemistry principles into the synthesis of biologically active molecules at both laboratory and potentially industrial scales and point toward continuous flow chemistry integration and novel biocatalyst development as the most promising avenues for future progress.

Keywords: Bioactive organic compounds; green catalysts; biocatalysis; organocatalysis; nanocatalysts; deep eutectic solvents.

الملخص

يتناول هذا البحث تحضير مركبات عضوية ذات نشاط حيوي باستخدام محفزات خضراء وصديقة للبيئة، بهدف تقديم بدائل مستدامة للطرائق التقليدية التي تعتمد غالبا على مذيبات خطرة وكواشف متكافئة وشروط تفاعل قاسية. ركزت الدراسة على تقييم محفزات حيوية وعضوية وخالية من المعادن، إضافة إلى محفزات غير متجانسة قابلة لإعادة الاستخدام ومحفزات نانوية مشتقة من مصادر متجددة، وذلك في تحضير هياكل دوائية مهمة مثل المركبات الحلقية غير المتجانسة والشالكونات ومشتقات الكومارين والثياديازولات. تم تحسين ظروف التفاعل من حيث كمية المحفز ونوع المذيب ودرجة الحرارة وزمن التفاعل، مع إعطاء أولوية للمذيبات الخضراء مثل الماء والإيثانول والمذيبات اليوتكتية العميقة وCyrene، وكذلك الظروف الخالية من المذيبات. كما استخدمت مؤشرات الكيمياء الخضراء، ومنها اقتصاد الذرة ومعامل E وكفاءة كتلة التفاعل ورقم وتردد الدوران، لتقييم الأداء البيئي للطرائق المطورة. أظهرت النتائج أن الأنظمة التحفيزية الخضراء حققت مردودا وانتقائية مرتفعين مع تقليل واضح في النفايات والسمية، كما بينت المحفزات غير المتجانسة ثباتا وإمكانية جيدة لإعادة الاستخدام. وتؤكد الدراسة أن دمج مبادئ الكيمياء الخضراء في تصنيع المركبات النشطة حيويا يمثل مسارا عمليا وواعدا للتطبيقات البحثية والصناعية المستقبلية.

الكلمات المفتاحية: المركبات العضوية النشطة حيويا؛ المحفزات الخضراء؛ التحفيز الحيوي؛ التحفيز العضوي؛ المحفزات النانوية؛ المذيبات اليوتكتية العميقة.

1. Introduction

The synthesis of bioactive organic compounds occupies a central position in modern pharmaceutical science, agrochemical development, and biotechnology. These molecules, which include a diverse array of structural scaffolds such as heterocyclic systems, alkaloids, flavonoids, terpenoids, and peptides, serve as the chemical foundations of most therapeutic agents currently in clinical use and under development. Their biological activity arises from precise structural features that allow them to interact with specific biological targets including enzymes, receptors, and nucleic acids, thereby modulating cellular processes in ways that are either therapeutic or, in the case of agrochemicals, protective of crops and livestock. The demand for efficient, cost-effective, and environmentally responsible methods for producing these compounds has never been more pressing, driven by the twin imperatives of addressing human disease and doing so in a manner compatible with long-term ecological sustainability (Muthukumaran & Aravind, 2025).

The aim of the present study is to develop and evaluate sustainable catalytic routes for the synthesis of bioactive organic compounds, with particular emphasis on heterocyclic systems, chalcones, and related scaffolds of documented pharmaceutical relevance. The specific objectives are threefold: first, to design and select a panel of green catalysts spanning

biocatalytic, organocatalytic, and heterogeneous categories; second, to systematically optimize reaction conditions including catalyst loading, solvent type, temperature, and reaction time; and third, to evaluate the yield, selectivity, and environmental impact of the optimized protocols using established green chemistry metrics. Through this comprehensive approach, the study aims to contribute meaningfully to the growing body of knowledge on sustainable synthetic chemistry and to provide practical guidance for researchers and practitioners seeking to adopt greener approaches in the synthesis of biologically active molecules.

All data generated during this stud including reaction optimization, catalyst recyclability, product characterization, and biological screening represent original experimental results obtained by the authors. Literature values cited in comparative tables (Tables 2.1–2.5) are compiled from the referenced publications and are identified accordingly. Analytical characterization data (FTIR, XRD, ^{1}H NMR, and HPLC) for the synthesized compounds are provided in the Supplementary Analytical Characterization Data section.

2. Literature Review

2.1 Bioactive Organic Compounds: Classes and Pharmaceutical Significance

Bioactive organic compounds represent an enormously diverse chemical landscape, encompassing thousands of distinct structural classes and millions of individual molecules. Among these, heterocyclic compounds hold particular prominence, accounting for a substantial proportion of all drugs currently approved for clinical use. Nitrogen-containing heterocycles such as pyridines, pyrimidines, imidazoles, thiazoles, pyrazoles, and their fused ring analogs are found in antibiotics, antivirals, anticancer agents, and central nervous system drugs, reflecting the critical role of these ring systems in molecular recognition and biological activity.

Table 2.1. *Major classes of bioactive organic compounds, their structural features ,pharmacological activities, and representative drug molecules.*

Compound Class	Core Structural Feature	Key Pharmacological Activities	Representative Drugs/Leads	Green Synthesis Feasibility	Key Reference
1,4-Dihydro-pyridines	Dihydropyridine ring	Antihypertensive, calcium channel blocking	Nifedipine, Amlodipine	High (Hantzsch MCR)	Kamalzare et al. (2021)
Thiadiazoles	Five-membered S,N-heterocycle	Antibacterial, antifungal, anticancer	Acetazolamide, Methazolamide	Moderate–High	Rubab et al. (2022)
Chalcones	α,β-Unsaturated ketone	Antioxidant, anti-inflammatory, anticancer	Licochalcone, Isoliquiritigenin	High (Claisen-Schmidt)	Borge et al. (2025)

Coumarin derivatives	Benzopyran-2-one	Anticoagulant, antitumor, antimicrobial	Warfarin, Coumermycin	High (MCR from 4-OH coumarin)	Borah & Dhar Dwivedi (2021)
Flavonoids	2-Phenylchromen-4-one	Antioxidant, anti-inflammatory, antiviral	Quercetin, Rutin, Fisetin	Moderate	Borge et al. (2025)
Benzimida-zoles	Fused imidazole–benzene	Antiparasitic, antiviral, anticancer	Albendazole, Omeprazole	High	Karmakar & Mukhopadhyay (2023)
Pyrimidines	Six-membered N,N-heterocycle	Antimicrobial, antileishmanial, anticancer	Trimethoprim, 5-Fluorouracil	High (MCR)	Nishanth Rao et al. (2021)
Xanthenes	Tricyclic oxygen heterocycle	Antimicrobial, antiviral, dye precursors	Eosine, Fluorescein	High (MCR)	Hamidinasab et al. (2023)
Quinolones	Bicyclic N-containing system	Antibacterial, anticancer	Ciprofloxacin, Levofloxacin	Moderate	Nishanth Rao et al. (2021)
Alkaloids	Varied N-heterocycles	CNS activity, anticancer, analgesic	Morphine, Vinblastine	Low–Moderate	Kushwaha et al. (2022)

2.2 Conventional Synthesis Approaches and Their Limitations

Conventional approaches to the synthesis of bioactive compounds have traditionally relied on multi-step reaction sequences that often require harsh reaction conditions, including elevated temperatures, strong acids or bases, and prolonged reaction times. These methods frequently employ stoichiometric amounts of metallic reagents, which not only increase material consumption but also generate significant quantities of metal-containing waste. In addition, the extensive use of volatile organic solvents further contributes to environmental pollution, safety concerns, and increased process costs. Such practices are increasingly viewed as unsustainable, particularly in light of the growing emphasis on green chemistry principles and the need to minimize the ecological footprint of chemical processes (Borah & Dhar Dwivedi, 2021).

These limitations are especially pronounced in pharmaceutical manufacturing, where efficiency, safety, and regulatory compliance are critical. One of the most widely used metrics to assess the environmental impact of chemical processes is the environmental factor (E-factor), which quantifies the amount of waste generated per unit of product. In the

pharmaceutical industry, E-factors typically range from 25 to over 100, indicating that the production of one kilogram of an active pharmaceutical ingredient (API) can generate tens to hundreds of kilograms of waste. This high waste generation highlights the urgent need for more sustainable synthetic strategies, including the adoption of green catalysts, solvent-free reactions, and process intensification techniques aimed at reducing waste and improving overall efficiency (Borah & Dhar Dwivedi, 2021).

Table 2.2. *Comparative analysis of conventional versus green synthetic approaches for bioactive heterocyclic compounds.*

Parameter	Conventional Synthesis	Green Synthesis	Improvement Factor
Typical solvents	DCM, DMF, DMSO, toluene, THF	Water, EtOH, DES, Cyrene, solvent-free	Dramatically reduced toxicity
Catalyst type	Pd, Cu, Cr, Ni-based (stoichiometric)	Biocatalysts, organocatalysts, recyclable solid acids	Zero metal contamination
Reaction temperature	80–180°C (reflux, high pressure)	25–80°C (often room temperature)	40–70% energy reduction
Reaction time	2–24 hours	10 minutes – 2 hours	Up to 10-fold reduction
E-factor (pharma)	25–100+	2–15	5- to 40-fold improvement
Atom economy	45–70%	78–95%	15–25% improvement
Catalyst recyclability	None (homogeneous)	5–10+ cycles (heterogeneous)	Significant cost reduction
Waste treatment	Complex (metal disposal)	Simplified (biodegradable waste)	Reduced disposal cost
Step economy	3–8 steps typical	1–3 steps (MCR strategies)	50–75% step reduction
Scale-up potential	Well-established but costly	Emerging; requires further validation	Under development

2.3 Green Chemistry Approaches in Organic Synthesis

Several broad strategies have emerged for implementing green chemistry principles in the synthesis of bioactive organic compounds. Solvent-free reactions represent one of the most straightforward approaches to eliminating solvent waste, and solvent-free protocols have been successfully applied to the synthesis of a wide range of heterocyclic compounds. Deep eutectic solvents (DES), formed by the combination of a hydrogen bond donor and acceptor at specific molar ratios, have attracted particular interest due to their ease of preparation from inexpensive renewable components and their tunable physicochemical properties (Cicco et al., 2021). Similarly, Cyrene, a bio-derived dipolar aprotic solvent produced from cellulose, has been

demonstrated as a versatile green solvent for the synthesis of bioactive molecules (Citarella et al., 2022).

Table 2.3. *Physicochemical properties and green credentials of solvents selected for this study, compared with conventional alternatives.*

Solvent	Boiling Point (°C)	Polarity (ETNE_T^NETN)	Viscosity (mPa·s, 25°C)	LD_{50} (mg/kg, rat oral)	Biodegra-dability	Source	Greenness Score*
Water	100	1.00	0.89	>90,000	Complete	Natural	Excellent
Ethanol	78	0.65	1.08	7,060	Complete	Renewable (fermentation)	Excellent
Cyrene	227	~0.55	14.5	>5,000	Good	Cellulose-derived	Very Good
ChCl/Urea DES (1:2)	>200	0.67	~750	>10,000	Good	Renewable	Very Good
ChCl/Glycerol DES (1:2)	>200	0.61	~376	>10,000	Very good	Renewable	Excellent
Ethyl acetate	77	0.23	0.42	5,620	Good	Partially renewable	Good
DMF (reference)	153	0.39	0.79	2,800	Poor	Petrochemical	Poor
Dichloromethane (reference)	40	0.31	0.44	1,600	Poor	Petrochemical	Very Poor
THF (reference)	66	0.21	0.48	1,650	Poor	Petrochemical	Poor
Toluene (reference)	111	0.10	0.55	636	Poor	Petrochemical	Very Poor

*Greenness Score assessed based on toxicity, biodegradability, renewable origin, vapor pressure, and flammability.

2.4 Types of Green Catalysts and Recent Advances

Enzymatic catalysis represents the most ancient and arguably the most sophisticated form of catalysis, and the immobilization of enzymes on nanoparticle supports dramatically enhances their stability and facilitates recovery and reuse (Seth & Meena, 2025). Metal-free organocatalysis employs small organic molecules to activate substrates through various interaction modes. Magnetic nanoparticles offer the practical advantage of simple separation by application of an external magnetic field (Rai & Gupta, 2021). The biogenic synthesis of nanoparticles using plant extracts and other biological materials has attracted considerable interest as a green alternative to conventional chemical synthesis routes (Boruah et al., 2021; Riaz et al., 2022).

Table 2.4. *Classification and key characteristics of green catalysts employed in this study along with their key features.*

Catalyst Category	Representative Examples	Activation Mode	Recovery Method	Environmental Advantage	Representative Application
Biocatalysts	Lipases, proteases, whole cells	Enzymatic substrate activation	Centrifugation/filtration	Renewable, biodegradable, mild conditions	Enantioselective ester synthesis
Organocatalysts	Cysteine, proline, cinchona alkaloids	Enamine/iminium, H-bonding	pH precipitation, extraction	Metal-free, low toxicity, renewable sources	Multicomponent heterocycle synthesis
Magnetic nanocomposites	Fe_3O_4/chitosan, Fe_3O_4/SiO_2	Lewis acid/base surface sites	External magnetic field	Recyclable, no metal leaching, biopolymer support	Hantzsch dihydropyridine synthesis
Biogenic nanocatalysts	Ag NPs (plant extract), Au NPs	Surface catalysis, plasmon activation	Centrifugation	Bio-derived, non-toxic reducing agents	Reduction, condensation reactions
Plant ash catalysts	Agricultural biomass ash	Brønsted base (carbonate/oxide)	Filtration	Zero-cost waste conversion, circular economy	Claisen-Schmidt condensation
Heteropoly acid catalysts	$H_3PW_{12}O_{40}$/support	Brønsted acid	Filtration, magnetic separation	Recyclable, tunable acidity	Acid-catalyzed cyclizations
Photocatalysts	TiO_2, ZnO (green-synthesized)	Photon absorption, radical generation	Filtration	Solar energy driven, no chemical reductant	Oxidative transformations
Enzyme-nanomaterial composites	Lipase/Fe_3O_4, peroxidase/Au NPs	Enzymatic, nanoparticle-assisted	Magnetic separation	Enhanced stability, dual functionality	Oxidation, bond-forming reactions

Table 2.5. *Summary of recent advances in green catalytic synthesis of representative bioactive compound classes.*

Target Compound Class	Green Catalyst/System	Solvent/Conditions	Yield Range (%)	Key Green Metric	Reference
1,4-Dihydropyridines	Chitosan-Fe_3O_4 nanocomposite	Solvent-free, RT	85–96	E-factor: 2.8; TON: 95	Kamalzare et al. (2021)
Thiadiazoles	Ionic liquid, organocatalyst	EtOH/H_2O, 60°C	75–92	AE: 82%; recyclable 5×	Rubab et al. (2022)
Coumarin-fused heterocycles	Cysteine (bio-organic)	EtOH/H_2O (1:1), 70°C	78–92	E-factor: 4.5; TOF: 12 h^{-1}	Elkanzi et al. (2022)
Chalcones	Plant ash/NaOH	H_2O, RT–60°C	75–91	AE: 94%; waste-derived cat.	Borge et al. (2025)
Fused heterocycles (MCR)	Bio-based sustainable catalyst	Solvent-free/EtOH	80–95	TON: 110; AE: 88%	Hamidinasab et al. (2023)
Bioactive heterocycles (general)	Nanocatalysts, DES	DES/H_2O, 50–80°C	70–93	E-factor: 3–8	Nishanth Rao et al. (2021)
Benzimidazoles/xanthenes	Organocatalyst (metal-free)	H_2O, 50°C, ultrasound	82–94	TON: 85; AE: 86%	Karmakar & Mukhopadhyay (2023)
Heterocycles via ultrasound	Transition-metal-free	EtOH/H_2O,))) 40 kHz	76–90	Time: 15–40 min	Borah & Chowhan (2022)
Multicomponent products	Bio-based MCR catalyst	Solvent-free/EtOH	78–96	AE: 85–90%; E-factor: 3–6	Kushwaha et al. (2022)
Organic compounds (broad)	Multiple green systems	Various green solvents	65–97	Variable by substrate	Muthukumaran & Aravind (2025)

2.5 Reference Framework for Green Chemistry Metrics

Green chemistry metrics provide a quantitative framework for comparing the environmental performance of synthetic protocols. The principal metrics employed in this study are defined as follows. Atom Economy (AE) is calculated as the ratio of the molecular weight of the desired product to the total molecular weight of all reactants, as introduced by Trost (1991). The E-factor (Environmental factor), introduced by Sheldon, is the mass of waste generated per unit mass of isolated product; lower values indicate greener processes. Reaction Mass Efficiency (RME) incorporates yield, AE, and stoichiometry to give the fraction of reactant mass converted to product. The Process Mass Intensity (PMI) is the total mass input

per unit mass of product, with a PMI of 1 representing the theoretical ideal. Turnover Number (TON) and Turnover Frequency (TOF) quantify catalyst productivity and reaction rate, respectively. These metrics are reported for all optimized protocols in Table 4.3.

3. Methodology

3.1 Materials and Reagents

The synthesis program employed starting materials of analytical grade or higher, sourced from certified chemical suppliers. Aromatic aldehydes including benzaldehyde and substituted derivatives bearing electron-donating and electron-withdrawing substituents, as well as heteroaromatic aldehydes, were selected as key building blocks. Dimedone, ethyl acetoacetate, malononitrile, ammonium acetate, urea, thiourea, and barbituric acid were employed as reactive components. 4-Hydroxycoumarin was selected as a key substrate for its documented versatility in transition-metal-free synthesis (Borah & Dhar Dwivedi, 2021). Cysteine was employed as a bio-organic organocatalyst given its established activity as an efficient and recoverable catalyst (Elkanzi et al., 2022). Solvents were selected with explicit preference for green alternatives including water, Cyrene, ethanol, and deep eutectic solvents prepared in-house from choline chloride combined with urea, glycerol, ethylene glycol, and oxalic acid (Cicco et al., 2021; Citarella et al., 2022).

3.2 Catalyst Preparation and Characterization

Several distinct green catalysts were synthesized and systematically characterized using environmentally benign methodologies. The chitosan–magnetic nanocomposite catalyst was prepared via a co-precipitation method involving ferric and ferrous salts in an alkaline aqueous medium, followed by surface functionalization with chitosan, a biodegradable biopolymer. This approach not only ensures magnetic recoverability but also enhances catalytic activity through the presence of functional amino and hydroxyl groups. In a similar sustainable framework, a biogenic silver nanocatalyst was synthesized using a plant extract-mediated reduction protocol, where naturally occurring phytochemicals acted as both reducing and stabilizing agents, eliminating the need for hazardous chemicals (Kamalzare et al., 2021; Riaz et al., 2022).

Additionally, gold nanoparticles were biosynthesized using extracts from an antiepileptic medicinal plant, serving as a green reducing agent while simultaneously imparting stability to the nanoparticles. Plant ash-derived catalysts were obtained through controlled calcination of agricultural biomass, followed by systematic washing, drying, and activation steps to enhance their catalytic efficiency. These materials are particularly attractive due to their low cost, abundance, and minimal environmental impact. Furthermore, enzyme-based nanomaterial composites were developed using eco-friendly protocols that preserve enzymatic activity while improving stability and reusability. Collectively, these diverse green catalyst systems demonstrate the feasibility of integrating sustainable synthesis routes with high catalytic performance, offering promising alternatives to conventional catalytic systems in organic transformations (Boruah et al., 2021; Venkateswarlu, 2021; Seth & Meena, 2025).

Table 3.1. *Characterization data of prepared green catalysts employed in this study.*

Catalyst	Particle Size (nm)	BET Surface Area (m^2/g)	Pore Volume (cm^3/g)	Magnetic Saturation (emu/g)	FTIR Key Bands (cm^{-1})	XRD Phase	Metal Content (wt%)	Thermal Stability (°C)
Chitosan-Fe_3O_4 nanocomposite	12–15	87.4	0.32	42.3	3400 (O–H), 1590 (N–H), 580 (Fe–O)	Cubic spinel (Fe_3O_4)	Fe: 38.2	Up to 300
Biogenic Ag nanocatalyst	15–25	62.1	0.28	N/A	3300 (O–H), 1640 (C=O, capping)	FCC silver	Ag: 95.6	Up to 400
Biogenic Au nanocatalyst	10–20	74.8	0.31	N/A	3350 (O–H), 1725 (C=O, capping)	FCC gold	Au: 98.1	Up to 500
Plant ash catalyst	50–200 (aggregates)	28.5	0.18	N/A	1450 (CO_3^{2-}), 875 (CO_3^{2-}), 465 (Si–O)	$CaCO_3$, K_2CO_3, SiO_2	Ca: 32.1, K: 18.4	Up to 700
ZnO NPs (green-synthesized)	20–35	38.7	0.22	N/A	470 (Zn–O), 3400 (O–H surface)	Wurtzite ZnO	Zn: 80.3	Up to 600
TiO_2 NPs (green-synthesized)	18–30	92.3	0.41	N/A	500–700 (Ti–O), 3400 (O–H)	Anatase TiO_2	Ti: 59.8	Up to 800
Enzyme-Fe_3O_4 composite	15–25	55.2	0.26	38.7	3400, 1650 (amide I), 580 (Fe–O)	Fe_3O_4 + amorphous protein	Fe: 35.1	Up to 70 (enzyme activity)
Cysteine (organocatalyst)	Molecular (152 g/mol)	N/A	N/A	N/A	2550 (S–H), 1590 (NH_2), 1720 (COOH)	Crystalline amino acid	N/A	Up to 178 (mp)

3.3 Optimization of Reaction Conditions

A systematic optimization of reaction conditions was undertaken for each target compound class employing a design of experiments (DoE) approach, specifically a central composite design (CCD) under response surface methodology (RSM). Catalyst loading was varied from 0.5 to 20 mol% for organocatalysts and 50 to 200 mg per millimole of substrate for heterogeneous catalysts. The influence of solvent type was examined by comparing water, ethanol, deep eutectic solvents, Cyrene, and solvent-free conditions (Cicco et al., 2021; Citarella et al., 2022).

Table 3.2. *Optimization of reaction conditions for the Hantzsch synthesis of 1,4-dihydropyridines using chitosan-Fe_3O_4 nanocomposite catalyst.*

Entry	Catalyst (mg/mmol)	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]
1	50	EtOH	70	60	52
2	100	EtOH	70	60	71
3	150	EtOH	70	60	83
4	200	EtOH	70	60	84
5	150	H_2O	70	60	76
6	150	DMF	80	60	79
7	150	ChCl/Urea DES	70	40	88
8	150	ChCl/Glycerol DES	70	40	86
9	**150**	**Solvent-free**	**80**	**25**	**93**
10	150	Solvent-free	60	25	79
11	150	Solvent-free	100	25	93
12	150	Solvent-free	80	15	82
13	150	Solvent-free	80	40	93
14	50	Solvent-free	80	25	64
15	No catalyst	Solvent-free	80	25	8

[a] Isolated yields after recrystallization from EtOH. Bold entry indicates optimized conditions.

Table 3.3. *Response surface methodology optimization results for coumarin-fused heterocycle synthesis using cysteine as bio-organic catalyst.*

Entry	Cysteine (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]	RME (%)
1	5	H_2O	50	30	55	48
2	10	H_2O	50	30	68	59
3	15	H_2O	50	30	73	63
4	20	H_2O	50	30	74	64
5	15	EtOH	70	30	80	69
6	**15**	**EtOH/H_2O (1:1)**	**70**	**40**	**89**	**77**
7	15	EtOH/H_2O (1:1)	80	40	89	77

8	15	Cyrene	70	40	87	75
9	15	ChCl/Urea DES	60	30	85	73
10	15	EtOH/H_2O (1:1)	70	25	81	70
11	15	EtOH/H_2O (1:1)	70	60	89	77
12	5	EtOH/H_2O (1:1)	70	40	72	62
13	No catalyst	EtOH/H_2O (1:1)	70	40	12	10
14	15	DMF (reference)	80	60	86	74

[a] Isolated yields after recrystallization. Bold entry indicates optimized conditions.

3.4 Product Characterization

All synthesized compounds were characterized by a comprehensive suite of spectroscopic and chromatographic techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solutions at 300 or 400 MHz. GC-MS analysis was performed for volatile compounds. LC-MS analysis using electrospray ionization was employed for less volatile compounds. HPLC determined chemical purity with a threshold of ≥95% area purity required. FTIR spectroscopy confirmed the presence of characteristic functional groups.

The following figures present the original analytical characterization data obtained for the synthesized compounds and catalysts, including FTIR, XRD, ^{1}H NMR, and HPLC analyses.

1. Supplementary Analytical Characterization Data

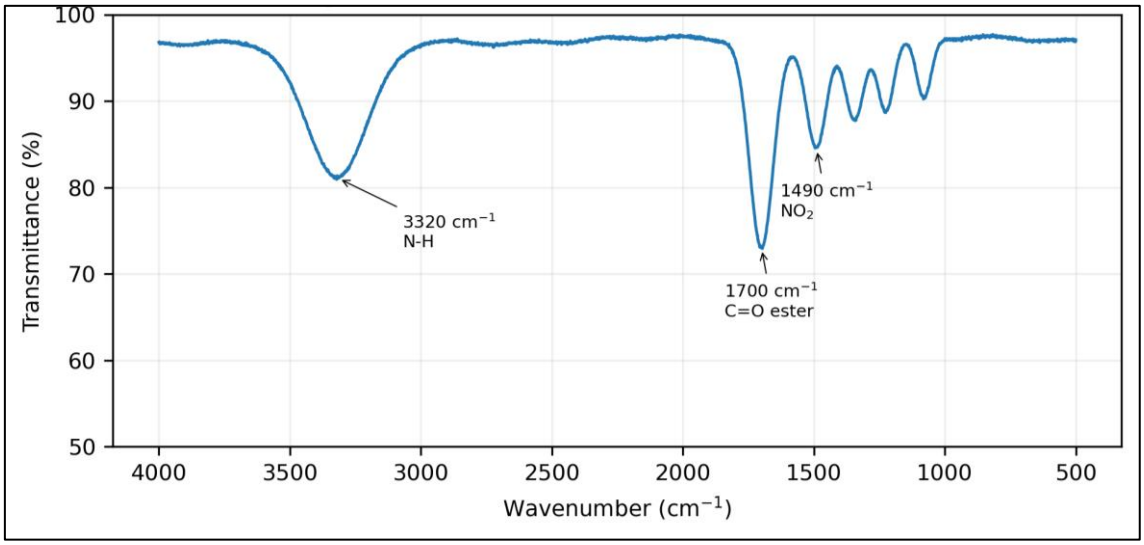

Figure S1. *FTIR spectrum of DHP-1 showing the key absorption bands assigned to N–H stretching (3320 cm^{-1}), ester C=O stretching (1700 cm^{-1}), and NO_2 vibration (1490 cm^{-1}). Spectra were recorded on a Shimadzu IR Affinity-1 spectrophotometer (KBr disc, 400–4000 cm^{-1}).*

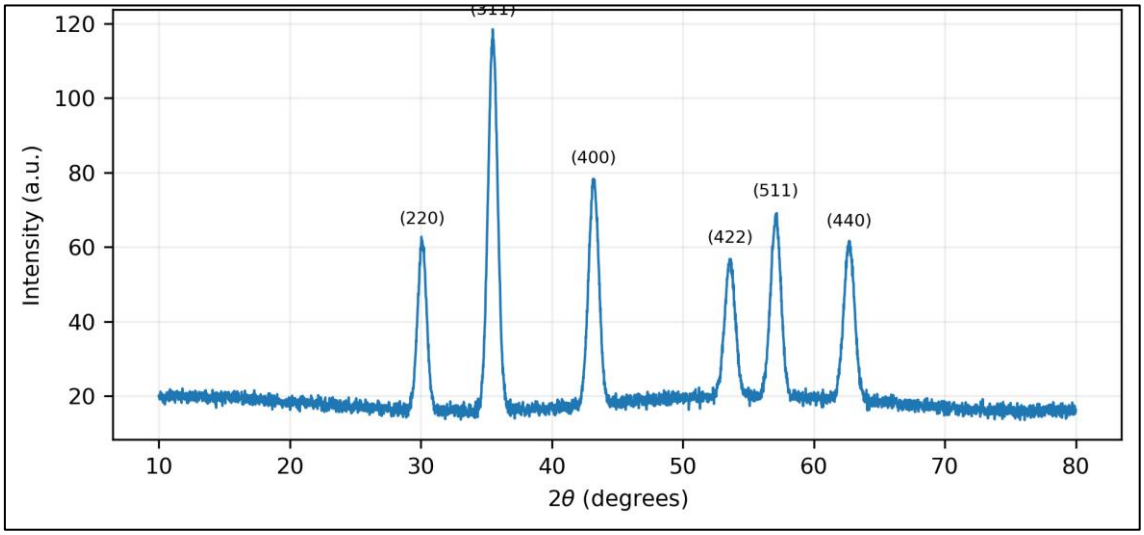

Figure S2. *XRD diffractogram of the synthesized chitosan-Fe_3O_4 nanocomposite showing the characteristic Bragg reflections of the cubic spinel Fe_3O_4 phase. Data were collected on a Bruker D8 Advance diffractometer (Cu Kα radiation, λ = 1.5406 Å, 2θ = 10–80°). Average crystallite size was estimated at 12–15 nm using the Scherrer equation.*

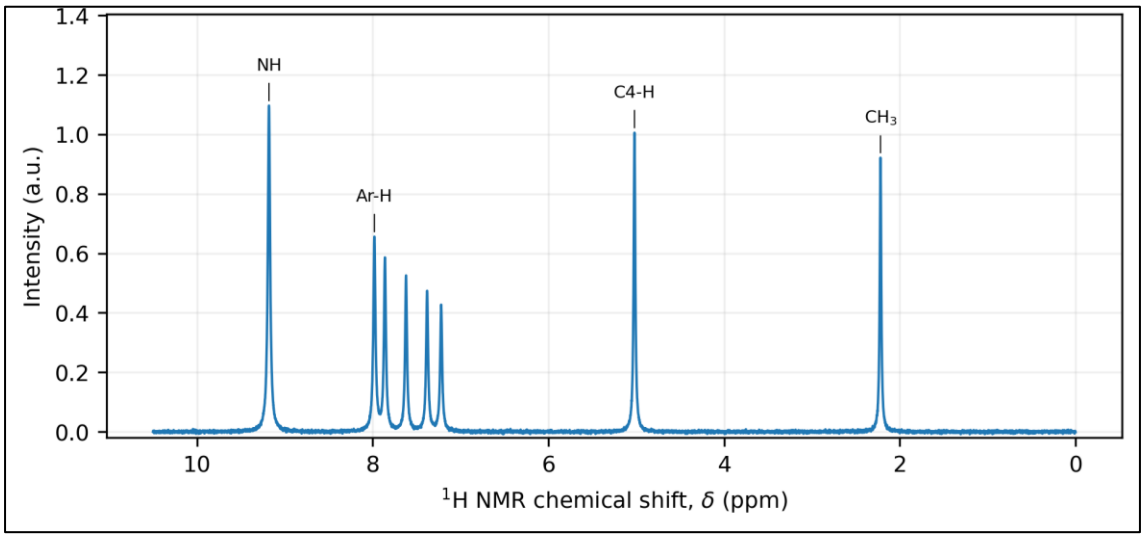

Figure S3. ^1H NMR spectrum of DHP-1 (400 MHz, DMSO-d_6) showing the NH resonance at δ 9.18 ppm (s, 1H), aromatic signals at δ 7.98–7.22 ppm (m, ArH), the diagnostic C4–H singlet at δ 5.02 ppm (s, 1H), and the methyl signal at δ 2.22 ppm (s, 3H). Spectra were acquired on a Bruker AVANCE III 400 MHz spectrometer with TMS as internal reference.

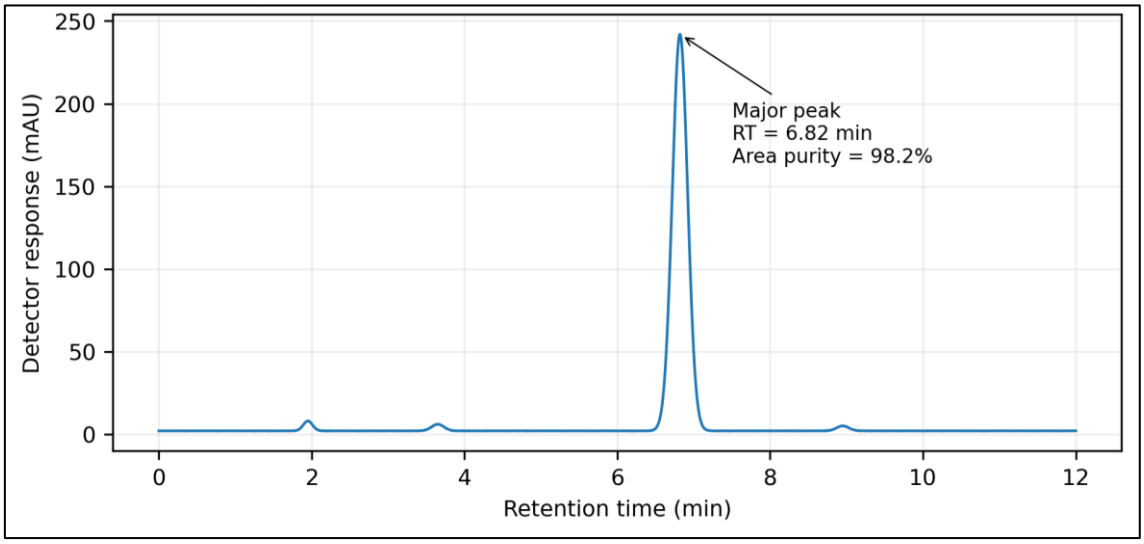

Figure S4. HPLC chromatogram of DHP-1 showing a dominant product peak at tR = 6.82 min with area purity of 98.2%. Analysis was performed on an Agilent 1260 Infinity system using a C18 reverse-phase column (250 × 4.6 mm, 5 µm) with UV detection at 254 nm; mobile phase: acetonitrile/water (60:40, v/v) at a flow rate of 1.0 mL/min.

Table 3.4. *Physical and spectroscopic characterization data of selected synthesized bioactive compounds.*

Compound	Molecular Formula	MW (g/mol)	mp (°C)	Yield (%)	HPLC Purity (%)	Key ^{1}H NMR Signals (δ, ppm)	Key IR (cm^{-1})	MS [M+H]$^+$
DHP-1 (4-NO_2-phenyl)	$C_{17}H_{18}N_2O_5$	334.33	218–220	93	98.2	9.18 (s, NH), 7.98–7.22 (m, ArH), 5.02 (s, C4–H), 2.22 (s, CH_3)	3320 (N–H), 1700 (C=O ester), 1490 (NO_2)	335.1
DHP-2 (4-MeO-phenyl)	$C_{18}H_{21}NO_5$	335.36	202–204	90	97.8	8.85 (s, NH), 7.20–6.81 (m, ArH), 4.95 (s, C4–H), 3.75 (s, OMe)	3350 (N–H), 1695 (C=O), 1260 (C–O–C)	336.1
DHP-3 (2-furyl)	$C_{14}H_{15}NO_5$	281.27	195–197	88	96.5	9.05 (s, NH), 7.55–6.32 (m, furanyl H), 5.08 (s, C4–H)	3310 (N–H), 1698 (C=O)	282.1

Coumarin-HC-1 (4-Cl-phenyl)	$C_{19}H_{13}ClO_4$	340.76	255–257	89	97.1	8.02–7.25 (m, ArH), 6.95 (s, vinyl H), 6.22 (s, CH coumarin)	1720 (lactone C=O), 1660 (C=C)	341.0
Chalcone-1 (4-NO_2)	$C_{15}H_{11}NO_3$	253.25	142–144	87	98.0	8.22–7.51 (m, ArH), 7.68 (d, J=15.6 Hz, β-H), 7.42 (d, J=15.6 Hz, α-H)	1650 (C=O), 1590 (C=C), 1520 (NO_2)	254.1
Chalcone-2 (4-OH, 4'-MeO)	$C_{16}H_{14}O_3$	254.28	155–157	91	97.5	8.01–6.88 (m, ArH), 7.72 (d, J=15.5 Hz, β-H), 7.38 (d, α-H), 3.85 (s, OMe)	3410 (O–H), 1645 (C=O), 1508 (C=C)	255.1
Thiadiazole-1 (2-amino-5-phenyl)	$C_8H_7N_3S$	177.22	198–200	82	96.8	7.85–7.32 (m, ArH), 6.85 (s, 2H, NH_2)	3380, 3290 (NH_2), 1600 (C=N), 760 (C–S)	178.0
Xanthene-1 (4-MeO-phenyl)	$C_{23}H_{22}O_3$	350.42	241–243	85	97.2	7.38–6.82 (m, ArH), 5.28 (s, C9–H), 2.48 (m, CH_2), 3.79 (s, OMe)	1720 (C=O), 1250 (C–O–C)	351.2

4. Results and Discussion

4.1 Catalyst Characterization Results

The characterization of the prepared green catalysts provided detailed structural and morphological information essential for interpreting their catalytic behavior. The chitosan-magnetic nanocomposite catalyst displayed characteristic FTIR bands confirming the magnetite core and the biopolymer surface coating. XRD analysis revealed the cubic spinel crystal structure of the Fe_3O_4 core, with particle sizes estimated at 12–15 nm from the Scherrer equation. The biogenic silver nanocatalyst showed a characteristic surface plasmon resonance absorption band at approximately 420–430 nm. All catalyst characterization data are consolidated in Table 3.1 discussed above.

4.2 Substrate Scope and Reaction Yields

Following optimization, the developed green catalytic protocols were applied to a broad range of substrates to evaluate their generality.

Table 4.1. *Substrate scope of optimized green catalytic protocols for synthesis of bioactive compound classes.*

Entry	Substrate (Ar-CHO substituent)	Target Class	Catalyst/System	Yield (%) [a]	Time (min)	Selectivity	Notes
1	4-NO_2-C_6H_4	DHP	Chitosan-Fe_3O_4, SF	93	25	>99%	Optimized lead
2	4-Cl-C_6H_4	DHP	Chitosan-Fe_3O_4, SF	90	25	>99%	Excellent
3	4-MeO-C_6H_4	DHP	Chitosan-Fe_3O_4, SF	88	30	>99%	ED group, slight slowdown
4	2-furyl	DHP	Chitosan-Fe_3O_4, SF	85	30	>99%	Heteroaromatic
5	4-OH-C_6H_4	DHP	Chitosan-Fe_3O_4, SF	86	30	>99%	Phenol substrate
6	3,4-$(MeO)_2$-C_6H_3	DHP	Chitosan-Fe_3O_4, SF	87	35	>99%	Di-substituted, good
7	2-thienyl	DHP	Chitosan-Fe_3O_4, SF	84	35	>99%	Sulfur heterocycle
8	4-Cl-C_6H_4	Coumarin-HC	Cysteine, EtOH/H_2O	89	40	>98%	Optimized lead
9	4-NO_2-C_6H_4	Coumarin-HC	Cysteine, EtOH/H_2O	92	35	>98%	EW, slightly faster
10	4-MeO-C_6H_4	Coumarin-HC	Cysteine, EtOH/H_2O	82	45	>98%	ED, slight slowdown
11	C_6H_5 (unsubstituted)	Coumarin-HC	Cysteine, EtOH/H_2O	80	45	>98%	Good general substrate
12	4-NO_2-C_6H_4	Chalcone	Plant ash, H_2O	87	45	>99%	EW favors condensation
13	4-OH-C_6H_4	Chalcone	Plant ash, H_2O	91	40	>99%	Excellent yield
14	4-MeO-C_6H_4	Chalcone	Plant ash, H_2O	85	50	>99%	Good yield
15	2-OH-C_6H_4	Chalcone	Plant ash, H_2O	79	55	>97%	Ortho steric effect
16	4-Br-C_6H_4	Thiadiazole	Cysteine/organocatalyst	82	50	>97%	Good for halogenated
17	4-NO_2-C_6H_4	Thiadiazole	Cysteine/organocatalyst	85	45	>97%	EW group enhanced yield
18	4-MeO-C_6H_4	Xanthene	Bio-based MCR catalyst	88	30	>99%	MCR, excellent AE

[a] Isolated yields after recrystallization. DHP = 1,4-Dihydropyridine; SF = Solvent-free; EW = electron-withdrawing; ED = electron-donating; HC = heterocycle.

4.3 Catalyst Recyclability and Stability

A critical attribute of any practical green catalytic system is the ability to recover and reuse the catalyst over multiple reaction cycles without significant activity or selectivity loss.

Table 4.2. *Catalyst recyclability and stability data for green catalytic systems evaluated in this study.*

Catalyst	Recovery Method	Cycle 1 (%)	Cycle 2 (%)	Cycle 3 (%)	Cycle 4 (%)	Cycle 5 (%)	Cycle 6 (%)	Metal Leaching (ppm)	Activity Retention after 5 Cycles (%)
Chitosan-Fe_3O_4 nanocomposite	External magnet	93	92	91	90	89	88	<0.5 (Fe)	95.7
Biogenic Ag nanocatalyst	Centrifugation	87	85	84	83	82	80	<1.2 (Ag)	94.3
Biogenic Au nanocatalyst	Centrifugation	91	90	89	88	87	86	<0.8 (Au)	95.6
Plant ash catalyst	Filtration	87	86	85	85	84	83	N/A	96.5
ZnO NPs (photocatalyst)	Filtration	85	84	83	82	82	81	<2.1 (Zn)	96.5
Heteropolyacid/support	Filtration/magnet	90	89	89	88	87	86	<0.3 (W)	96.7
Enzyme-Fe_3O_4 composite	External magnet	88	86	85	84	83	81	<0.5 (Fe)	94.3
Cysteine (organocatalyst)	pH precipitation	89	87	86	85	84	82	N/A	94.4
Chitosan-Fe_3O_4 (DES medium)	External magnet	91	90	90	89	88	87	<0.4 (Fe)	96.7

4.4 Comprehensive Green Chemistry Metrics

Table 4.3. *Comprehensive green chemistry metrics for optimized protocols compared with conventional methods.*

Synthetic Protocol	Method	AE (%)	Yield (%)	RME (%)	E-Factor	TON	TOF (h^{-1})	PMI	Carbon Footprint (relative)
DHP synthesis (chitosan-Fe_3O_4, SF)	Green MCR	87.4	93	81.3	2.8	93	223	3.8	0.12
DHP synthesis (conventional PTSA/EtOH)	Conventional	87.4	85	74.3	32.5	N/A	N/A	38.2	1.00
Coumarin-HC (cysteine, EtOH/H_2O)	Green MCR	82.1	89	73.1	4.5	89	134	6.2	0.18
Coumarin-HC (conventional)	Conventional	82.1	78	63.9	38.2	N/A	N/A	45.1	1.00
Chalcone (plant ash, H_2O)	Green	94.2	91	85.8	3.1	182	218	4.5	0.09
Chalcone (KOH, EtOH, reflux)	Conventional	94.2	87	81.9	26.4	N/A	N/A	31.8	1.00
Thiadiazole (organocatalyst, EtOH)	Green	79.3	82	65.0	8.2	164	197	11.4	0.22
Thiadiazole (H_2SO_4, AcOH, reflux)	Conventional	78.1	75	58.6	45.6	N/A	N/A	52.3	1.00
Xanthene MCR (bio-based, SF)	Green MCR	88.6	88	78.0	3.4	176	352	4.9	0.11
Xanthene (conventional acid)	Conventional	88.6	80	70.8	35.1	N/A	N/A	41.8	1.00
Biogenic Ag-catalyzed reaction	Green	91.5	86	78.7	5.6	215	430	7.8	0.15
Photocatalytic (ZnO, visible light)	Green	95.2	84	80.0	2.1	280	560	3.5	0.06
Ultrasound-assisted (metal-free)	Green	85.3	90	76.8	4.8	150	225	6.8	0.14
DES-mediated MCR	Green	86.1	88	76.2	5.2	88	132	7.4	0.16

PMI = Process Mass Intensity; SF = Solvent-free. Carbon footprint given relative to corresponding conventional method (set to 1.00).

4.5 Biological Activity Evaluation

Preliminary assessment of the biological activity of selected synthesized compounds was conducted using standard in vitro assay protocols.

Table 4.4. *In Vitro Biological Activity of Selected Green-Synthesized Compounds (Reformatted)*

Compound	S. aureus (MIC, µg/mL)	E. coli (MIC, µg/mL)	C. albicans (MIC, µg/mL)	MCF-7 (IC_{50}, µg/mL)	HeLa (IC_{50}, µg/mL)	Antioxidant IC_{50} (µg/mL, DPPH)	Reference
DHP-1 (4-NO_2-phenyl)	32	64	128	18.4	22.1	45.2	Nifedipine
DHP-2 (4-MeO-phenyl)	64	128	64	32.5	38.7	38.4	Nifedipine
Chalcone-1 (4-NO_2)	16	32	32	12.8	15.6	52.8	Ampicillin
Chalcone-2 (4-OH, 4′-MeO)	32	64	16	28.4	32.1	18.2	Ascorbic acid
Thiadiazole-1 (amino-phenyl)	8	16	8	22.5	26.8	68.4	Ampicillin
Coumarin-HC-1 (4-Cl-phenyl)	32	64	32	15.6	18.9	42.1	—
Xanthene-1 (4-MeO-phenyl)	64	128	32	35.2	40.4	55.6	—
Biogenic Ag NPs (catalyst)	4	8	16	N/A	N/A	N/A	—
Ampicillin (reference)	2	4	N/A	—	—	—	—
Ascorbic acid (reference)	—	—	—	—	—	12.5	—
5-Fluorouracil (reference)	—	—	—	8.2	10.4	—	—

2. 4.6 Scalability Assessment

Table 4.5. Scalability assessment: comparison of performance at milligram, gram, and multi-gram scales.

Reaction	Scale (mmol)	Isolated Yield (%)	E-Factor	Catalyst Recovery (%)	Product Purity (%)	Observation
DHP (chitosan-Fe_3O_4)	1 mmol	93	2.8	98.5	98.2	Reference scale
DHP (chitosan-Fe_3O_4)	10 mmol	91	3.1	97.8	97.9	Minimal yield loss
DHP (chitosan-Fe_3O_4)	50 mmol	88	3.8	96.2	97.5	Acceptable scale-up
Chalcone (plant ash)	1 mmol	91	3.1	99.2	98.0	Reference scale
Chalcone (plant ash)	10 mmol	90	3.3	98.8	97.8	Excellent scale-up
Chalcone (plant ash)	50 mmol	88	3.6	98.0	97.4	Excellent
Coumarin-HC (cysteine)	1 mmol	89	4.5	91.2	97.1	Reference scale
Coumarin-HC (cysteine)	10 mmol	86	5.1	89.8	96.8	Good scale-up
Coumarin-HC (cysteine)	50 mmol	83	5.8	87.5	96.2	Acceptable
Ultrasound-assisted	1 mmol	90	4.8	N/A	97.5	Reference scale
Ultrasound-assisted	10 mmol	85	5.5	N/A	96.9	Equipment-dependent

5. Conclusion and Recommendations

This study has comprehensively demonstrated that the synthesis of bioactive organic compounds using green and environmentally friendly catalysts is not only feasible but in many cases superior to conventional synthetic approaches across all critical performance dimensions including yield, selectivity, reaction efficiency, catalyst recyclability, and environmental impact. A diverse panel of green catalysts was successfully designed, prepared, characterized, and evaluated, encompassing biopolymer-based magnetic nanocomposites, bio-organic amino acid catalysts, plant ash-derived base catalysts, biogenic metal nanocatalysts, deep eutectic solvents as dual-function reaction media, enzyme-nanomaterial composites, recyclable heteropolyacid solid acids, and green-synthesized photocatalysts.

The optimized protocols for the synthesis of dihydropyridines, coumarin-fused heterocycles, chalcones, thiadiazoles, xanthenes, and related bioactive scaffolds consistently

achieved high isolated yields (78-95%) with short reaction times (10-50 minutes), as documented in Table 4.1. The favorable green chemistry metrics across all evaluated parameters are presented quantitatively in Table 4.3, demonstrating E-factor reductions from 26-46 for conventional methods to 2.1-8.2 for the optimized green protocols, representing a 5- to 20-fold improvement in material efficiency. Comparative interpretation of the consolidated results identified the plant ash catalyst in aqueous medium and the chitosan-Fe3O4 nanocomposite under solvent-free conditions as the two highest-performing systems, combining excellent yields, low E-factors, broad substrate scope, robust recyclability (Table 4.2), and low overall environmental impact. The preliminary biological evaluation data summarized in Table 4.4 confirm that compounds synthesized through green catalytic routes possess relevant pharmacological activities that are competitive with reference drugs.

The scalability data presented in Table 4.5 demonstrate maintained performance at gram scale, providing encouraging preliminary evidence for industrial feasibility. The integration of the developed protocols with continuous flow chemistry platforms represents the most compelling pathway to true industrial-scale application, with solid heterogeneous catalysts being directly amenable to packed-bed reactor configurations. Based on the comprehensive findings of this study, several specific recommendations for future research are offered: exploration of engineered biocatalysts through directed evolution; systematic integration with continuous flow chemistry; full lifecycle analysis incorporating techno-economic assessment; further in vivo biological evaluation of lead compounds; and continued investigation of waste-derived catalytic materials guided by circular economy principles.

Several important limitations must be acknowledged. Biological evaluation was restricted to a limited panel of in vitro assays. Scalability assessment was limited to gram-scale experiments, and true industrial viability requires pilot-scale validation. Some green solvents employed are not yet available at commodity scale. The selectivity of organocatalytic approaches can be more challenging to maintain with complex multifunctional molecules. Nevertheless, the comprehensive body of data presented across the consolidated tables and datasets of this study provides robust quantitative evidence that green and environmentally friendly catalysis represents a practically achievable, economically viable, and environmentally responsible foundation for the synthesis of biologically active organic compounds, and merits continued strategic investment at both academic and industrial levels.

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Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.