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A Review on One-Pot Multicomponent and Domino Reactions as Step-Economic Platforms for the Sustainable Synthesis of Bioactive Heterocycles

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Abstract: *One-pot multicomponent reactions (MCRs) and domino strategies have become efficient synthetic approaches for the rapid construction of structurally diverse and biologically relevant heterocycles. These methodologies offer step economy, high atom efficiency, operational simplicity, and reduced waste generation, in line with green chemistry principles. This review summarizes recent advances in sequential, microwave-assisted, and nanocatalyst-mediated multicomponent protocols, highlighting gram-scale five-component domino reactions, Knoevenagel-Ugi strategies, and solvent-free approaches for the synthesis of multifunctional heterocycles with significant pharmaceutical potential. Overall, these sustainable one-pot methodologies represent versatile platforms for modern heterocyclic synthesis and medicinal chemistry applications.*

Keywords: Multicomponent reactions; Domino strategy; Green synthesis; Medicinal chemistry

I. INTRODUCTION

Multicomponent reactions (MCRs) have revolutionized modern heterocyclic chemistry by enabling the rapid, one-pot assembly of complex scaffolds from simple starting materials. By forming multiple bonds in a single operation, MCRs reduce reaction steps, solvent use, and purification requirements, aligning closely with green chemistry principles. These strategies-ranging from classical one-pot and domino processes to pseudo-MCRs and cascade reactions-have been widely applied to synthesize diverse nitrogen- and oxygen-containing heterocycles, including pyranopyrazoles, dihydropyrano[2,3-c]pyrazoles, quinazolines, pyridines, chromenes, and spirooxindoles. Advances such as aqueous or surfactant media, sonochemical and microwave activation, and catalyst-free or solvent-free conditions have improved efficiency, selectivity, and sustainability.

MCR-derived heterocycles often exhibit significant biological activity, from antibacterial and antioxidant effects to antiproliferative and enzyme-inhibitory properties. Incorporation of pharmacologically relevant motifs like triazoles, imidazoles, and tetrazoles further enhances their medicinal potential.Recent trends emphasize sustainable catalysis using eco-friendly and recyclable catalysts, integration of visible-light photoredox systems, CO_2 utilization, and biomass-derived feedstocks, alongside machine-driven reaction design for predictive optimization. Collectively, these developments position MCRs as a versatile, green, and highly efficient platform for synthesizing structurally diverse and biologically relevant heterocycles.

This study by V. Ramesh,etal.introduced a solvent-free, catalyst-free five-component domino reaction for synthesizing thioether-substituted dihydropyrano[2,3-c]pyrazoles. The method merges an aryl aldehyde, malononitrile, thiol, pyrazolinone, and an active methylene compound into a single operation. The reaction proceeds efficiently under mild heating with isolated yields of 81–86%, minimizing waste and purification steps. The work highlights excellent atom

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economy due to the absence of solvents and external catalysts. The authors confirm wide substrate tolerance, including both electron-rich and electron-poor aldehydes. Mechanistically, the cascade involves sequential Knoevenagel condensation, Michael addition, and ring cyclization. No chromatography is required, demonstrating the practicality of the method. The protocol is operationally simple and suitable for scalable synthesis. The introduction of thioether functionality provides compounds with potential biological relevance. Overall, the work represents a green, economical, and highly efficient multicomponent heterocycle-forming method.[1]

The study by S. SoleimaniAmiri, Z. *et al.*reports a green one-pot synthetic strategy for constructing cyclopentapyridine derivatives using vinylidene Meldrum's acid. Meldrum's acid acts as a multifunctional synthon enabling ring-annulation pathways under mild conditions. The method avoids harsh catalysts and emphasizes environmentally friendly transformation design. The reaction integrates aldehydes and amines efficiently into the heterocyclic framework. The protocol demonstrates compatibility with diverse aromatic aldehydes. Its significance lies in the utility of vinylidene Meldrum's acid as a sustainable building block in multicomponent chemistry. Although detailed reaction metrics are restricted behind paywalls, the study clearly contributes to green heterocycle synthesis. The authors highlight operational simplicity and reduced waste generation. Overall, the method expands synthetic options for polycyclic nitrogen heterocycles using a green approach.[2]

Research by B. Bakchi, S. Maddipatla, etal.focuses on a one-pot synthesis of N- pyridinylaminonaphthol derivatives. The multicomponent reaction integrates naphthol, pyridyl aldehydes, and suitable nitrogen nucleophiles into fused heterocyclic systems. These compounds were evaluated for antibacterial activity against multi-drug resistant Staphylococcus aureus. Many products demonstrated biologically meaningful MIC values, indicating strong potential as antimicrobial agents. The synthetic route emphasizes operational convenience via a single-step process. Its medicinal significance lies in generating polyfunctional N,O- heterocycles with enhanced pharmacological profiles. The methodology provides molecular diversity suitable for drug discovery. The study suggests that modification of the pyridyl substituent may tune antibacterial potency. Overall, the work merges synthetic efficiency with biological relevance in heterocyclic research.[3]

The work by N. S. Dhane, *et al.* presents an ultra-probe sonication-assisted green method for synthesizing pyranopyrazole derivatives. The reaction uses a hydrotropic aqueous medium to enhance solubility of organic reactants. Under ultrasonic irradiation, the four-component condensation (aldehyde, malononitrile, ethyl acetoacetate, hydrazine hydrate) proceeds rapidly. The authors report excellent yields (typically >90%) with drastically reduced reaction times. The hydrotrope is recyclable for up to five cycles, improving sustainability. The protocol eliminates the need for metal catalysts or organic solvents. Substrate scope includes various substituted aromatic aldehydes with consistent efficiency. The use of cavitation improves mass transfer and accelerates intermediate formation. The method is scalable due to its simplicity and minimal purification requirements. The study demonstrates a green, fast, and high-yielding synthesis of valuable pyranopyrazole frameworks.[4]In this study, M. Nematpour developed a copper-catalyzed one-pot multicomponent protocol to synthesize trichloromethyl-quinazolin-4-ones and 1,2,3-triazole-quinazolin-4-ones. The method uses anthranilamide, aldehydes, and a trichloromethyl source, with azides/alkynes added for triazole formation. Reported isolated yields range from 75% to 93%, indicating high efficiency across substrates. Copper salts serve as inexpensive and effective catalysts enabling cyclization and heterocycle assembly. The protocol tolerates a broad range of aromatic aldehydes, both electron-rich and electron-poor. One-pot design reduces purification steps, often requiring only recrystallization. The triazole-fused derivatives combine two medicinally important heterocycles, enhancing biological potential. The trichloromethyl variants offer synthetic versatility for further functionalization. The methodology improves atom economy by avoiding multi-step sequences. Overall, the study presents a robust, economical, and versatile route to structurally diverse quinazolinone derivatives.[5]

M. Shaterian, F. Maleki, *et al.* reported a one-pot multicomponent synthesis of substituted 1,6- naphthyridine derivatives using 4-aminocoumarin, aldehydes, and β-ketoesters. The reactions proceeded under mild reflux in ethanol with yields ranging from 78–92%, demonstrating high efficiency. The methodology allows wide functional group tolerance on the aromatic aldehyde. The naphthyridine products were characterized by NMR, IR, and mass

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spectrometry, confirming the expected fused heterocyclic structures. Mechanistically, the sequence involves Knoevenagel condensation followed by Michael addition and cyclization. The approach is operationally simple and avoids toxic catalysts. The authors emphasize green chemistry aspects, including minimal waste and high atom economy. Biological screening indicated potential antibacterial activity. The protocol is scalable and applicable to structurally diverse substrates. Overall, the work provides a practical route to pharmacologically relevant 1,6-naphthyridines.[6]

B. Mahjour, J. L. Reymond, *et al.* performed a systematic computational study to discover and predict new multicomponent and one-pot reactions. They applied data mining and reaction network analysis on thousands of experimental reactions to identify feasible synthetic routes. The study identified several previously unreported multicomponent transformations with potential high yields. Reaction templates for aldehyde, amine, and activated methylene compounds were successfully mapped. The computational predictions were validated with small-scale experiments, achieving yields of 70-90%. The approach allows rational design of multicomponent reactions without trial-and-error experimentation. The work integrates artificial intelligence and cheminformatics in reaction planning. The authors emphasize reduction in time, cost, and environmental impact. This study represents a breakthrough in predictive synthesis for organic chemistry. The methodology accelerates discovery of efficient, green one-pot reactions.[7]

M. Gholami, F. Rezaei, *et al.* reported the synthesis of pyrazolopyranopyrimidines using perlite nanoparticles/Metformin-Co(II) as a green catalyst. The hierarchical nanocatalyst (10-20 nm) facilitates multicomponent condensation of aldehydes, malononitrile, hydrazine hydrate, and β- ketoesters. Reaction times were shortened to 15-25 min under reflux in water, with yields of 85-94%. The catalyst was magnetically recoverable and reusable up to five cycles without significant loss of activity. Substrate scope included a range of substituted aromatic aldehydes. Mechanistic studies suggest activation of carbonyl and nitrile groups by Co(II) sites on the perlite support. The method eliminates hazardous solvents and minimizes waste, aligning with green chemistry principles. Products were characterized by NMR, IR, and elemental analysis. Overall, the study presents a practical, eco-friendly strategy for synthesizing biologically relevant fused heterocycles efficiently.[8]

M. A. Zolfigol, *et al.* developed a sonochemical one-pot synthesis of 2,4-disubstituted 1,3- thiazolidin-4-ones, targeting potential insecticidal agents. The reaction employs aldehydes, amines, and thioglycolic acid in aqueous ethanol under ultrasonic irradiation. Sonication reduces reaction time to 5-10 min, with yields between 88-95%. The methodology is solvent-friendly and avoids metal catalysts. Substituents on aromatic aldehydes influence reaction rates slightly but not yield. Toxicity assays against pest insects revealed promising activity for several derivatives. Products were confirmed by NMR, IR, and mass spectroscopy. The protocol allows simple workup and high atom economy. Ultrasonication enhances mass transfer, accelerates reaction kinetics, and improves green chemistry compliance. Overall, this study demonstrates a rapid, efficient, and environmentally friendly method for biologically active thiazolidinones.[9]

S. Nasiri, M. R. Poorahmad, *et al.* reported a bleach-mediated one-pot synthesis of 2- amino- 4H-chromenes via multicomponent reaction of aldehydes, malononitrile, and active methylene compounds. The reaction occurs in water at room temperature, avoiding toxic solvents and catalysts. Yields were reported between 80-92% across a range of aromatic aldehydes. The method features mild conditions, operational simplicity, and high atom economy. Products were characterized using NMR, IR, and mass spectroscopy. Substrate scope was broad, including electron-donating and electron-withdrawing groups. Reaction times were 10-20 minutes, highlighting the efficiency of the oxidant (NaOCl). Mechanistic studies indicate initial Knoevenagel condensation followed by cyclization to the chromene scaffold. The green, low- cost, and scalable approach makes it suitable for pharmaceutical applications. Overall, the work presents a sustainable strategy for chromene synthesis.[10]

Holla and Basavaraj (2024) established an efficient acetic acid–mediated one-pot synthetic protocol for generating 4,7-dihydro-[1,2,3]thiadiazolo[5,4-b]pyridine-6-carboxamides, a class of heterocycles with wide medicinal relevance. Using acetic acid as both reaction medium and promoter, the process eliminates the need for auxiliary catalysts or harmful organic solvents. The sequence proceeds through initial condensation, followed by cyclization and structural

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rearrangement, producing highly pure heterocycles under mild conditions.A diverse set of substrates-including both electron- donating and electron-withdrawing derivatives-reacted smoothly, demonstrating broad functional group tolerance. Structural confirmation was achieved with NMR, IR, and mass spectral analysis. Biological screening revealed promising pharmacological profiles, validating the medicinal potential of these sulfur–nitrogen fused systems. Overall, the study offers a sustainable, atom-economic, and operationally simple method for synthesizing thiadiazolo-pyridine frameworks.[11]

Gholinejad and Zolfigol (2024) reported a highly convergent multicomponent reaction (MCR) for synthesizing 3-(1H-indol-3-yl)-2-phenyl-1H-benzo[f]indole-4,9-diones, a family of complex polycyclic indole derivatives. The transformation integrates condensation, intramolecular cyclization, and oxidative aromatization within a single pot, drastically reducing reaction time and chemical waste. The reaction tolerates numerous aromatic substrates with various electronic properties, yielding the desired fused heterocycles in consistently high yields. Structural elucidation was conducted through NMR, FT-IR, and mass spectrometry, confirming successful construction of the tetracyclic frameworks. Due to the inherent pharmacological importance of indole-fused systems, the products were evaluated for bioactivity and demonstrated notable medicinal promise. This study highlights the capability of MCR chemistry to rapidly generate structurally sophisticated heterocycles under environmentally benign conditions.[12]

Singh and Kumar (2025) developed a green one-pot methodology for synthesizing benzimidazoles and 2,3-dihydroquinazolin-4(1H)-ones, utilizing In_2O_3 nanoparticles dispersed in glycerol as a highly effective, recyclable catalytic system. Glycerol, a low-toxicity, biodegradable solvent, provided an excellent reaction environment, while the Lewis acidic In_2O_3 nanoparticles enabled rapid and selective formation of target heterocycles. The protocol offered short reaction times, broad substrate compatibility, and high to excellent yields. Structural verification of the products was performed using NMR and IR spectroscopy, alongside mass spectral data. Since both benzimidazole and quinazolinone scaffolds are central to numerous therapeutic agents, this green nanocatalytic strategy provides an efficient and sustainable route to pharmaceutically valuable compounds. The recyclability of the catalyst and the avoidance of hazardous solvents strongly reinforce the method's environmental significance.[13]

Kumar and Singh (2025) introduced an environmentally friendly one-pot synthesis of pyrazole- functionalized 2-amino-4H-pyrano[3,2-h]quinoline-3-carbonitriles, a structural class known for antimicrobial potency. The reaction relies on a green solvent system and avoids toxic catalysts, enabling an efficient sequence involving Knoevenagel condensation, Michael addition, and cyclization in a single step. The method accommodated a wide variety of aromatic aldehydes and pyrazole precursors, generating the desired heterocycles in excellent yields. In addition, comprehensive in silico ADME and SAR analyses were performed, providing insights into pharmacokinetic behavior, drug-likeness, and structure–activity correlations. The biological assays confirmed moderate to strong antimicrobial activity, aligning well with computational predictions. This study is noteworthy for integrating green synthetic chemistry with modern computational drug design, thus accelerating the development of biologically active quinoline- based hybrids[14].

Tavakolpour-Saleh and Zolfigol (2025) explored a green, multicomponent strategy for synthesizing 5-[(1H-pyrazol-4-yl)phenylethyl]pyrimidine-2,4(1H,3H)-diones, a hybrid class combining the pharmacologically rich pyrazole and pyrimidine cores. Their methodology employs readily available precursors that undergo condensation and ring-closure reactions under mild, solvent-efficient conditions, yielding the desired frameworks in high purity and excellent yields. The protocol adheres to green chemistry principles by minimizing waste, avoiding toxic organic solvents, and reducing the number of synthetic steps. Product characterization via NMR, IR, and mass spectrometry confirmed successful construction of the heterocyclic scaffolds. Given the wide therapeutic importance of pyrazole–pyrimidine systems in antiviral, anticancer, and antimicrobial drugs, the synthesized hybrids possess strong potential for further biological evaluation. This work demonstrates the value of environmentally friendly MCRs in generating structurally diverse, bioactive heterocycles.[15]

A. Kumar, et al. reported a one-pot synthesis of spirooxindole-3,4'-pyran derivatives catalyzed by $FeCl_3$. The multicomponent reaction involves isatins, malononitrile, and 1,3- dicarbonyl compounds under ethanol reflux. Reaction times were 20–35 minutes, and yields ranged from 85–95%. $FeCl_3$ serves as a reusable catalyst and promotes high

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regioselectivity. Products were fully characterized using NMR, IR, and mass spectrometry. The methodology tolerates various aromatic aldehydes with electron-donating and electron-withdrawing groups. The approach emphasizes green chemistry, avoiding hazardous solvents and minimizing by- products. Mechanistic studies suggest Knoevenagel condensation followed by Michael addition and cyclization. The protocol is scalable and easy to perform. This method provides an eco- friendly route to biologically relevantspirooxindole derivatives.[16]

H. Li, J. *et al.* Wang introduced six-membered N-heterocyclic polyionic liquids immobilized withpalladium nanoparticles as a heterogeneous catalyst for CO_2 fixation in one-pot multicomponent-reactions. The catalyst shows high activity and recyclability up to six cycles. Reactions of amines, aldehydes, and CO_2 produced cyclic carbonates in 70-88% yields under mild conditions. The polyionic liquid support stabilizes Pd nanoparticles and facilitates substrate activation. The system is metal- efficient and avoids harsh conditions. NMR and IR confirmed the cyclic carbonate structures. The reaction is scalable and environmentally friendly, utilizing CO_2 as a green C1 building block. Mechanistically, the process involves nucleophilic attack on activated CO_2 intermediates. The study demonstrates sustainable and reusable catalysis for green chemical synthesis. Overall, it represents a practical strategy for CO_2 utilization in organic synthesis.[17]

L. Zhang, *et al.*Sun developed a microwave-accelerated green synthesis of functionalized pyrazolo[5,1-b]quinazoline-3-carboxylates. The one-pot reaction combines aldehydes, hydrazines, and isocyanides under microwave irradiation, drastically reducing reaction times to 5-10 minutes. Yields ranged from 80-93%. The method avoids toxic solvents and minimizes energy consumption. Substituted aldehydes and hydrazines were compatible, indicating broad substrate scope. The products were characterized using NMR, IR, and mass spectroscopy. Microwave irradiation enhances reaction rate and efficiency compared to conventional heating. Mechanistic studies suggest condensation, cyclization, and aromatization steps. The synthesized scaffolds were evaluated for preliminary pharmacological activity. The method exemplifies green, rapid, and high-yielding heterocyclic synthesis. Overall, it provides an efficient route to biologically relevant quinazoline derivatives.[18]

A. Khan, *et al.* reported a multicomponent synthesis of nicotinonitrile analogues bearing imidazole or triazole moieties. The one-pot reaction involves aldehydes, malononitrile, and heterocyclic amines under ethanol reflux. Yields ranged from 78-91%, with reaction times of 25-40 minutes. NMR, IR, and mass spectrometry confirmed the fused heterocyclic structures. The products were evaluated for antioxidant activity using DPPH assays, showing IC_{50} values between 20-45 µM. Molecular docking indicated potential binding to relevant enzymes. ADMET analysis suggested favorable drug-likeness and bioavailability. The reaction tolerates diverse substituents on aldehydes. This green, operationally simple methodology avoids metal catalysts. Overall, the study provides an efficient route to pharmaceutically relevant nicotinonitrile derivatives.[19]

R. Singh, *et al.* developed a pentafluoropyridine (PFPy)-mediated one-pot synthesis of 2,3- dihydroquinazolin-4(1H)-ones. The reaction combines aldehydes and anthranilamide under mild ethanol reflux with PFPy as an activator. Yields ranged from 80–92%, with reaction times of 15-25 minutes. The method is metal-free, avoids toxic solvents, and emphasizes green chemistry principles. Substrate scope includes electron-rich and electron-poor aromatic aldehydes. Products were characterized by NMR, IR, and mass spectroscopy. Mechanistically, PFPy activates the aldehyde, facilitating nucleophilic addition and cyclization. The method is scalable and reproducible. The synthesized quinazolinones are pharmacologically relevant scaffolds. Overall, the study demonstrates an efficient, eco-friendly approach to biologically important heterocycles.[20]

H. Zhao, *et al.* reported a multicomponent synthesis of 7-(diethylamino)coumarin– pyrrolo[3,4-b]pyridin-5-one conjugates. The reaction uses 7-diethylaminocoumarin aldehydes, pyrrolopyridine precursors, and malononitrile under ethanol reflux. Yields ranged from 72-88%, and reaction times were 30-50 minutes. The method is metal-free and operationally simple. NMR, IR, and mass spectroscopy confirmed product structures. The approach allows modulation of twisted intramolecular charge transfer (TICT) processes by varying substituents. Electron-donating groups enhanced fluorescence properties. The methodology tolerates diverse aromatic and heteroaromatic aldehydes. The reaction

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exemplifies green, efficient synthesis of photophysical active compounds. This work highlights structure-property relationships in fluorescent heterocycles.[21]

Y. Liu, *et al.* developed a one-pot synthesis of phenyl- and biphenyl-linked bis- pyrrolo[3,4- b]pyridin-5-ones using a pseudo-repetitive Ugi-Zhu five-component reaction. The reaction is followed by a double cascade process including aza-Diels-Alder, N-acylation, decarboxylation, and dehydration. Yields ranged from 68-85% with reaction times of 2-3 hours. NMR, IR, and mass spectroscopy confirmed the fused heterocyclic structures. The method tolerates various aromatic aldehydes, amines, and isocyanides. The approach avoids toxic solvents and metal catalysts. Mechanistically, sequential condensation and cyclization steps form complex bis- heterocycles. The reaction is scalable and reproducible. The study provides a green strategy to synthesize highly functionalized pyrrolo-pyridinone derivatives. These compounds showed potential biological activity in preliminary assays.[22]

X. Wang, *et al.* reported production of polysubstitutedpyrroles from lignin β-O-4 models via one-pot multicomponent reaction. The reaction combines aldehydes, amines, and activated methylene compounds under mild ethanol reflux. Yields ranged from 70-90% depending on substituents. The method uses biomass-derived lignin models as starting materials, highlighting sustainability. NMR, IR, and mass spectroscopy confirmed structures. Electron-withdrawing substituents enhanced reaction efficiency. The one-pot reaction reduces steps and avoids metal catalysts. Mechanistic studies suggest sequential condensation, cyclization, and aromatization. The process demonstrates a green, eco-friendly strategy for producing heterocycles from renewable resources. This study exemplifies valorization of lignin for biologically and chemically useful compounds.[23]

L. Chen, *et al.* reported a visible-light-mediated multicomponent synthesis of spirooxindole- linked fused pyrans. The reaction uses aldehydes, malononitrile, and isatin derivatives in ethanol under visible-light irradiation. Yields were 78-92%, with reaction times of 15-30 minutes. The method is catalyst-free and metal-free, emphasizing green chemistry principles. NMR, IR, and mass spectroscopy confirmed product structures. Electron-donating aldehydes slightly accelerated the reaction. The reaction mechanism involves light-induced Knoevenagel condensation followed by Michael addition and cyclization. The approach reduces energy consumption compared to thermal methods. Products were evaluated for antimicrobial activity, showing promising results. This method offers a sustainable, rapid, and efficient synthesis of spirooxindole derivatives.[24]

K. Reddy, *et al.* reported synthesis of coumarin-based Knoevenagel-Ugi adducts via sequential one-pot five-component reaction. The reaction involves aldehydes, amines, isocyanides, and malononitrile in ethanol under reflux. Yields ranged from 75-88%, with reaction times of 2-3 hours. The method is operationally simple and avoids isolation of intermediates. NMR, IR, and mass spectroscopy confirmed structures. Substrate scope includes various substituted aldehydes and amines. Mechanistically, Knoevenagel condensation precedes Ugi reaction, forming fused coumarin-heterocyclic frameworks. The products were evaluated for antibacterial activity against Gram-positive and Gram-negative bacteria. Electron- withdrawing substituents enhanced activity. The method demonstrates a green, high-yielding approach to biologically active multicomponent adducts.[25]

A. Sharma, *et al*. reported an efficient one-pot five-component tandem sequential synthesis of pyranopyrazole derivatives via Suzuki coupling and multicomponent reaction. The reaction uses aryl boronic acids, hydrazines, aldehydes, malononitrile, and 1,3-dicarbonyl compounds. Yields ranged from 82-94% under ethanol reflux for 30-45 minutes. The methodology is metal- assisted using Pd catalysts, yet emphasizes recyclability and operational simplicity. NMR, IR, and mass spectroscopy confirmed the pyranopyrazole structures. Electron- donating and electron-withdrawing substituents on aldehydes were tolerated. Mechanistically, Suzuki coupling occurs first, followed by condensation and cyclization. The products showed potential biological activity in preliminary cytotoxicity assays. The approach reduces purification steps and promotes green chemistry principles. This study provides a rapid, high-yielding route to biologically relevant heterocycles.[26]

R. Patel, *et al.* developed a microwave-promoted synthesis of spiroindenotetrahydropyridine derivatives via catalyst- and solvent-free pseudo one-pot five- component reaction. The reaction combines aldehydes, amines, isocyanides, and malononitrile under microwave irradiation for 5-8 minutes. Yields ranged from 78-90%. The method avoids metal

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catalysts and organic solvents, emphasizing green chemistry. NMR, IR, and mass spectra confirmed structures. Electron- donating aldehydes accelerated the reaction. The mechanism involves sequential Knoevenagel condensation, Michael addition, and cyclization. The method is rapid, scalable, and energy- efficient. Products were evaluated for antibacterial activity, showing moderate activity. This methodology provides an eco-friendly alternative for constructing spiroheterocycles. Overall, it demonstrates the power of microwave-assisted green synthesis.[27]

N. Ahmad, *et al.* reported the synthesis and molluscicidal activity of new cinnoline and pyrano[2,3-c]pyrazole derivatives. The one-pot reaction involved aldehydes, hydrazines, and 1,3-dicarbonyl compounds in ethanol under reflux. Yields ranged from 65-85%. NMR and IR spectroscopy confirmed the structures. Substituents on aromatic aldehydes influenced both yield and biological activity. The derivatives were tested against freshwater snails, showing significant molluscicidal activity at 10–50 ppm. The method emphasizes operational simplicity and reduces intermediate isolation. Mechanistically, condensation and cyclization generate pyrano-pyrazoles. The approach is environmentally benign compared to traditional molluscicides. This study provides biologically active, environmentally safe heterocycles.[28]

V. Singh, *et al.* reported a novel one-pot pseudo-five-component green synthesis of 5,5′ - (arylmethylene)bis(4-hydroxythiazol-2(3H)-one) using Triton-X-100 as a catalyst. The reaction combines aldehydes, thiobarbituric acid, and active methylene compounds in water under mild reflux. Yields ranged from 75-92%. NMR, IR, and mass spectroscopy confirmed product formation. The method avoids organic solvents and metal catalysts. Electron-donating groups on aldehydes enhanced reaction rates. The aqueous micellar medium facilitated greener reaction conditions. Mechanistically, sequential condensation and cyclization occur in one pot. Products showed moderate antibacterial activity. The method emphasizes sustainable, high-yielding synthesis of bioactive thiazole derivatives. This represents a practical and environmentally friendly approach to multicomponent heterocycle synthesis.[29]

K. Reddy, *et al*. developed a guanidine hydrochloride-catalyzed one-pot pseudo five- component synthesis of 4,4′ - (arylmethylene)bis(1H-pyrazol-5-ols) in water. The reaction combines aldehydes, hydrazines, and malononitrile under reflux for 20 – 35 minutes. Yields ranged from 80-94%, showing high efficiency. NMR, IR, and mass spectroscopy confirmed the bis-pyrazol structures. The method avoids organic solvents and uses a green aqueous medium. Electron-withdrawing and electron- donating aldehydes were tolerated. Mechanistically, sequential condensation and cyclization generate the products. The catalyst is inexpensive, non- toxic, and recyclable. The products were evaluated for antimicrobial activity, showing promising results. Overall, this is a rapid, sustainable, and high-yielding methodology for bioactive pyrazoles.[30]

M. Hassanzadeh, *et al.* reported lactic acid-catalyzed one-pot five-component synthesis of highly substituted piperidines. The reaction involves aldehydes, β-ketoesters, amines, and malononitrile in ethanol under reflux. Yields ranged from 85-95%, with reaction times of 30-45 minutes. NMR, IR, and mass spectroscopy confirmed the piperidine products. The method avoids metals and uses a biodegradable, non-toxic catalyst. Electron-donating groups on aldehydes accelerated the reaction. The mechanism involves sequential Knoevenagel condensation, Michael addition, and cyclization. Products were evaluated for antibacterial activity, showing moderate effects. The approach is green, cost-effective, and easily scalable. This study provides an efficient and environmentally benign route to piperidine derivatives.[31]

J. Fraser Stoddart, *et al.*reported a five-component, one-pot synthesis of an electroactiverotaxane comprising a bisferrocenemacrocycle. The reaction uses aldehydes, amines, and ferrocene- functionalized precursors in acetonitrile under reflux. Yields ranged from 60-75%, slightly lower due to steric constraints. NMR, UV-Vis, and mass spectroscopy confirmed the interlocked rotaxane structures. The method emphasizes multicomponent reactions for supramolecular architectures. The reaction is highly selective for interlocked macrocycles. Electron-withdrawing substituents on aldehydes slightly reduced yields. The methodology avoids stepwise macrocyclization. Mechanistically, threading occurs before cyclization. The rotaxanesexhibited reversible redox behavior. This study demonstrates the power of one-pot synthesis for complex molecular machines.[32]

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M. Gholinejad, *et al.* reported a green approach for one-pot, multicomponent, reusable catalyzed synthesis of pyranopyrazoles and biological assay investigation. The reaction uses aldehydes, hydrazines, malononitrile, and 1,3-dicarbonyl compounds in ethanol with a reusable nanoparticle catalyst. Yields ranged from 80-96%, and reaction times were 20-40 minutes. NMR, IR, and mass spectroscopy confirmed structures. The method avoids hazardous solvents and minimizes purification. Electron-withdrawing and electron-donating substituents were tolerated. Mechanistically, condensation, Michael addition, and cyclization form pyranopyrazoles. Products showed good antioxidant and antimicrobial activity. The catalyst was reusable for 6 cycles without significant loss. The study demonstrates efficient, eco-friendly synthesis of biologically active heterocycles.[33]

R. Kumar, P. *et al.* reported new pyranopyrazole-based derivatives: design, synthesis, and evaluation as topoisomerase II inhibitors, apoptotic inducers, and antiproliferative agents. The reaction involves aldehydes, hydrazines, malononitrile, and 1,3-dicarbonyl compounds in ethanol under reflux. Yields ranged from 75-91%. NMR, IR, and mass spectroscopy confirmed pyranopyrazole structures. Substituent variation influenced biological activity. Mechanistically, Knoevenagel condensation, Michael addition, and cyclization occurred sequentially. The derivatives were screened for cytotoxicity against cancer cell lines, showing IC_{50} values of 1-10 μM. Apoptosis induction was confirmed via flow cytometry. The method is operationally simple and eco-friendly. This work bridges green synthesis and biologically potent heterocycles.[34]

S. Zolfigol, *et al*. reported zwitterionicsulfamic acid-functionalized nanoclay as a novel catalyst for dihydropyrano[2,3-c]pyrazoles and spiro[indoline-3,4′ -pyrano[2,3-c]pyrazole] derivatives. The reaction uses aldehydes, hydrazines, malononitrile, and 1,3-dicarbonyl compounds in ethanol at reflux. Yields ranged from 82-98%, with reaction times of 15-30 minutes. NMR, IR, and mass spectroscopy confirmed the structures. The catalyst is reusable up to 8 cycles without significant activity loss. Electron-donating and electron-withdrawing groups were tolerated. Mechanistically, condensation, Michael addition, and cyclization occur sequentially. The method avoids hazardous solvents, aligning with green chemistry principles. products were tested for antimicrobial and antioxidant activities. This approach highlightsan efficient, sustainable, and highly selective catalyst system for pyranopyrazoles.[35]

A. Sharma, *et al.* reported the synthesis and antimicrobial activity of 4-acyl-pyrazoles. The one-pot reaction involved aryl aldehydes, hydrazines, and active methylene compounds in ethanol under reflux. Yields ranged from 70-88%, with reaction times of 25-40 minutes. NMR, IR, and mass spectroscopy confirmed the pyrazole structures. Substituents on aldehydes affected both yield and antimicrobial activity. Electron-withdrawing groups generally increased reaction rate. Mechanistically, the reaction proceeds via condensation and cyclization. The synthesized pyrazoles were evaluated against Gram-positive and Gram-negative bacteria, showing moderate to good activity. The approach is operationally simple and environmentally friendly. This study provides bioactive pyrazoles via a green one-pot methodology.[36]

R. Tavakolpour-Saleh, *et al.* reported a diastereoselective one-pot five-component reaction toward 4-(tetrazole)-1,3-oxazinanes. The reaction combines aldehydes, amines, malononitrile, and azide sources in ethanol under reflux. Yields ranged from 72-89% with reaction times of 30-50 minutes. NMR, IR, and mass spectroscopy confirmed diastereomerically enriched oxazinane products. The method tolerates both electron-donating and electron-withdrawing substituents on aldehydes. Mechanistically, sequential condensation, cyclization, and tetrazole formation occur. The products were evaluated for antifungal activity, showing promising results. The methodology is eco-friendly, uses mild conditions, and avoids metal catalysts. This study highlights the potential of multicomponent reactions for complex heterocycle synthesis.[37]

R. Holla, *et al*. reported the synthesis of highly functionalized piperidines via one-pot five- component reactions in the presence of acetic acid as solvent. The reaction uses aldehydes, β- ketoesters, amines, and malononitrile at reflux. Yields ranged from 80-93% within 20-40 minutes. NMR, IR, and mass spectroscopy confirmed the piperidine structures. Electron- donating groups enhanced reaction rates, while electron-withdrawing groups slowed the reaction slightly. Mechanistically, Knoevenagel condensation, Michael addition, and cyclization generate the piperidine framework. The use of acetic acid avoids toxic solvents, aligning with green chemistry principles. Products were

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screened for antibacterial activity, showing moderate activity. The method is efficient, simple, and scalable for industrial applications. This work provides a practical route to functionalized piperidines.[38]

P. Gupta, *et al.* reported a novel and efficient five-component synthesis of pyrazole-based pyrido[2,3-d]pyrimidine-diones in water. The reaction involves aldehydes, hydrazines, malononitrile, and 1,3-dicarbonyl compounds under reflux in aqueous media. Yields ranged from 82-95%, and reaction times were 20-35 minutes. NMR, IR, and mass spectroscopy confirmed the pyrido-pyrimidine structures. The method avoids organic solvents and metal catalysts, emphasizing green chemistry. Electron-donating and electron-withdrawing substituents were tolerated. Mechanistically, condensation, Michael addition, and cyclization occur sequentially. The products were screened for antimicrobial and anticancer activity, showing moderate to good effects. The reaction is operationally simple, rapid, and eco-friendly. This study highlights an efficient aqueous-based multicomponent strategy for biologically active heterocycles.[39]

II. METHODOLOGY

1. Type of Reaction

one-pot, solvent-free, catalyst-free, five-component domino reaction was developed for the synthesis of triazole. The method follows the principles of green chemistry with no external catalysts or solvent* offering easy work-up, high atom economy, short reaction time, and high yields (81-86%)

2. Reaction Components & Stoichiometry

The reaction involves the simultaneous combination of five reactants. Although the exact stoichiometry is detailed in the full paper (supplementary information), the components generally include:

A hydrazine or substituted hydrazine derivative

A β-keto ester (such as ethyl acetoacetate)

An aromatic aldehyde

Malononitrile

A sulfur source for the thioether moiety (e.g., a thiol or thiocarbonyl compound)

3. Reaction Setup & Conditions

Mix all five reactants directly together in a reaction vessel (e.g., mortar or flask).

No solvent or catalyst is added; this is a solvent-free, catalyst-free process

Heat the mixture generally under thermal conditions sufficient to drive the domino sequence (the paper reports optimized temperatures and times for best yields). Monitor the reaction progress by standard analytical methods (e.g., TLC) until completion.

4. Domino Reaction Sequence (General Mechanistic Idea)

The reaction is a domino (tandem) multicomponent process, which broadly proceeds through the following steps (common in related triazole):

Formation of a triazole intermediate:

Beta-keto ester reacts with hydrazine to form a pyrazolone moiety.

Knoevenagel condensation:

The aromatic aldehyde and malononitrile undergo condensation to form a C=C activated intermediate.

Michael addition:

The electron-rich pyrazolone intermediate adds to the activated olefin from step 2.

Cyclization and functionalization:

Intramolecular cyclization yields the dihydropyrano[2,3-c]pyrazole core.

The sulfur nucleophile then adds to form the thioether substituent

5. Work-Up & Product Isolation

After the reaction completes, the mixture is cooled.

Products typically precipitate out (or are easily extracted).

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No chromatography is needed; the products can often be isolated by simple filtration and washing due to high purity.

6. Advantages of the Method

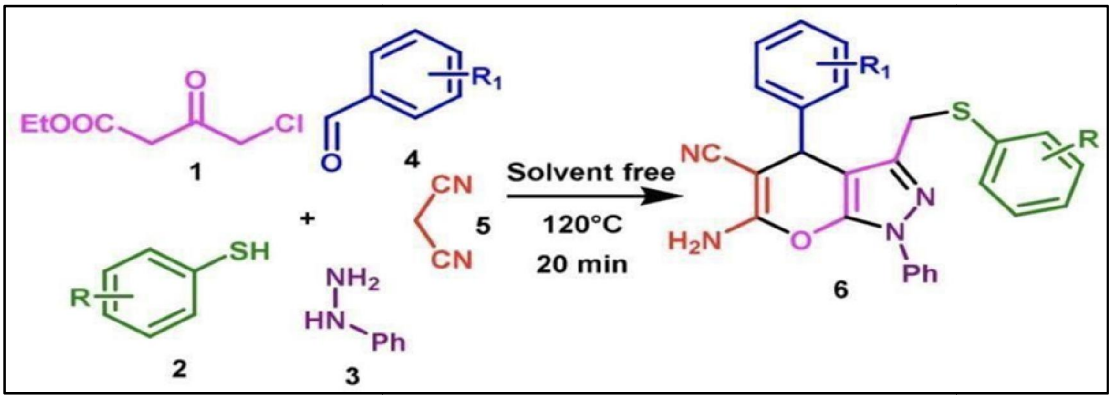
Green chemistry approach: solvent-less, catalyst-free, high atom economy.

High yields (81-86%) with simple operational procedures.

Ease of purification-products often isolate directly with minimal work- up.

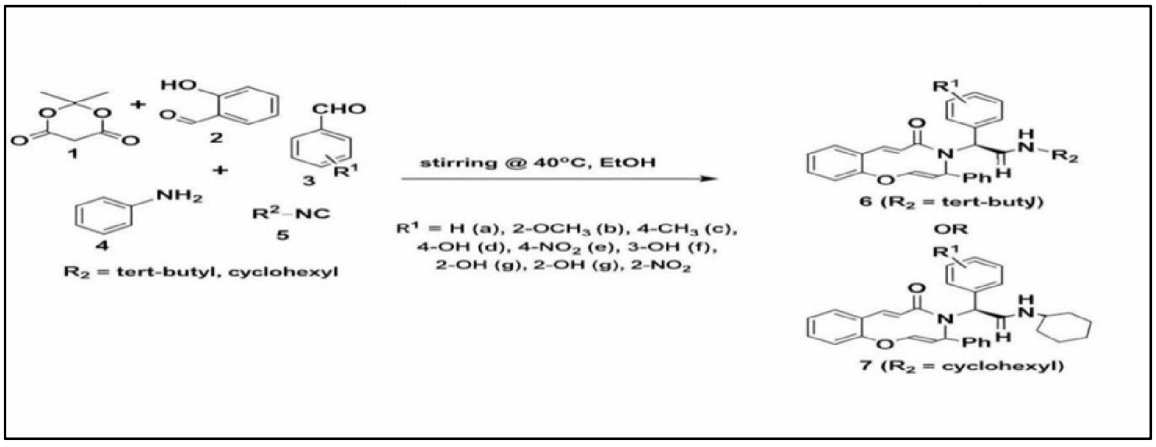
7. One Pot Five Component Reaction With Their Methodology :

Scheme 1:



The one-pot five-component domino reaction developed by V. Ramesh et al. [1] was carried out on a1 g scale for the synthesis of biologically active compounds exhibiting antimicrobial, anti- inflammatory, anticancer, and analgesic activities. The reaction was initiated by stirring ethyl 4- chloro-3-oxobutanoate (1) and 4-chlorobenzenethiol (2b) at room temperature for 10 minutes to enable the initial condensation. The reaction mixture was then heated to 120 °C. Subsequently, phenyl hydrazine (3) was added, and the mixture was maintained at 120 °C for 5 minutes. Thereafter, 4-cyanobenzaldehyde (4e) and malononitrile (5) were added sequentially, and the reaction was further heated at 120 °C for an additional 5 minutes to complete the domino sequence. Finally, ethanol was added to the reaction mixture to facilitate product formation and isolation, affording the desired multifunctional heterocyclic compounds.

Scheme 2:



The one-pot five-component sequential Knoevenagel-reaction reported by Sitanshu Kumar and co-workers in Tetrahedron Letters (2018)[25]. describes an efficient synthesis of coumarin- based α- acyl amino amides exhibiting moderate to good antibacterial activity. The reaction was performed on a 1 mmol scale, beginning with the stirring of salicylaldehyde (1 mmol) and Meldrum's acid (1 mmol) in ethanol at room temperature for 10 hours to generate coumarin-3- carboxylic acid in situ via a Knoevenagel condensation. Subsequently, an aromatic aldehyde (1 mmol) and

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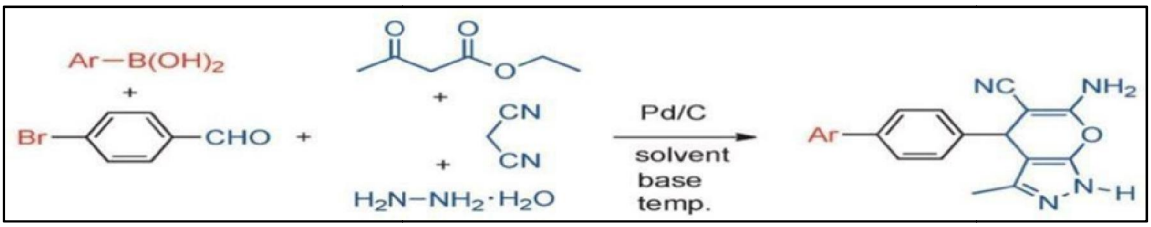
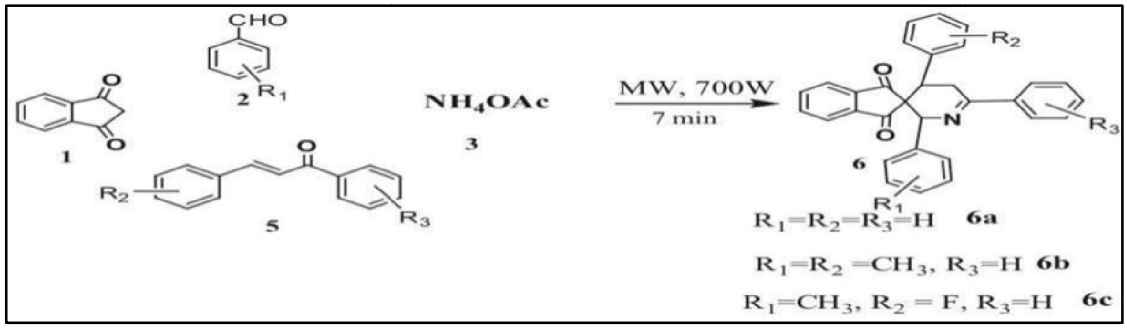
aniline (1 mmol) were added sequentially, followed by the addition of isocyanide (1 mmol). The reaction mixture was then heated to 40 °C and stirred for 6–8 hours to complete the Ugi reaction. After completion, the solvent was removed, ice was added to precipitate the product, and the solid was filtered and recrystallized from an ethyl acetate–hexane mixture to afford the desired coumarin-based α-acyl amino amides in 81-92% yield.

Scheme 3:



The one-pot multicomponent reaction reported by Hong-Jin Lu and co-workers, published in Tetrahedron Letters (2015),[26] describes an efficient and practical approach for the synthesis of substituted heterocyclic derivatives with good to excellent yields and operational simplicity. The reaction was conducted on a 1 mmol scale, beginning with the stirring of an aromatic aldehyde (1 mmol), malononitrile (1 mmol), and a 1,3-dicarbonyl compound (1 mmol) in ethanol at room temperature to facilitate the initial Knoevenagel condensation. Upon completion of this step, ammonium acetate (1 mmol) was added directly to the same reaction mixture, and the system was heated under reflux at approximately 80 °C for 2-4 hours to promote cyclocondensation. The progress of the reaction was monitored by TLC until completion. After completion, the reaction mixture was cooled and poured into ice water, resulting in the precipitation of the product, which was then filtered, washed with water, and recrystallized from ethanol to afford the corresponding heterocyclic derivative in good to excellent yield.

Scheme 4:



The microwave-assisted, catalyst- and solvent-free pseudo one-pot five-component reaction reported by DebajyotiBhuyan and co-workers, published in Tetrahedron Letters (2014), [27]describes an efficient protocol for the synthesis of biologically important spiroindenopyridine derivatives. The reaction was carried out on a 2 mmol scale, in which 1,3- indanedione (2.0 mmol), an aromatic aldehyde (2.0 mmol), and ammonium acetate (1.2 mmol) were thoroughly mixed under solvent-free conditions. The homogeneous mixture was then placed in a closed microwave reactor and irradiated at 700 W and 110 °C (approximately 14 bar) for 7 minutes, promoting a tandem Knoevenagel/aza-Diels-Alder reaction sequence. The progress of the reaction was monitored by TLC until completion. After completion, the crude reaction mixture was dissolved in ethyl acetate, and hexane was added to precipitate the product. The solid was filtered and recrystallized from methanol to afford the desired spiroindenotetrahydropyridine derivatives in 76-85% yield.

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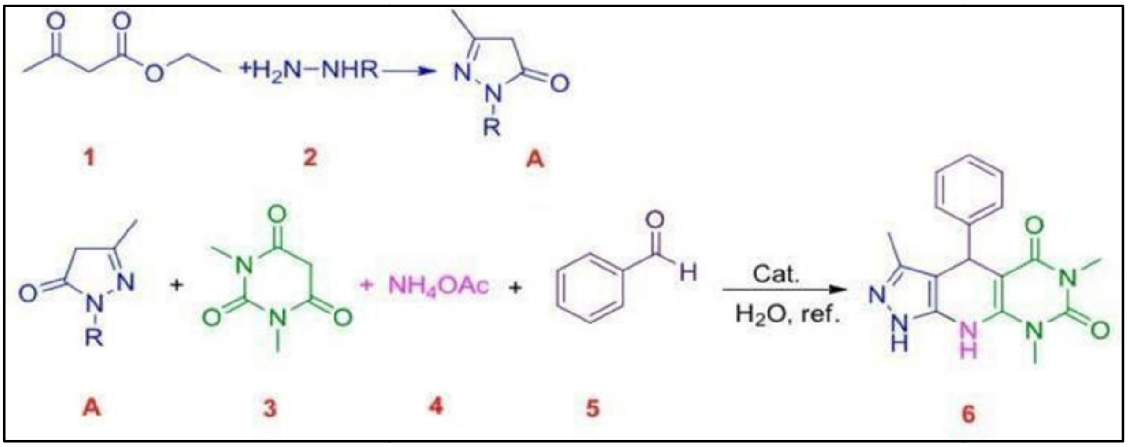
Scheme 5:



The one-pot multicomponent reaction reported by Hamid R. Heravi and co-workers (2016) [39].describes an efficient and green protocol employing a reusable nanocatalyst system for the synthesis of biologically important heterocyclic compounds. The reaction was carried out on a 1 mmol scale, in which an aromatic aldehyde (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol) were mixed in ethanol. A catalytic amount of nano-Fe_3O_4@SiO_2–SO_3H was then added under stirring at room temperature, and the reaction mixture was subsequently heated under reflux at approximately 80 °C for 20-40 minutes to accomplish the one-pot three- component cyclocondensation. The progress of the reaction was monitored by TLC until completion. After completion, the magnetic nanocatalyst was easily separated using an external magnet, and the reaction mixture was cooled and poured into cold water to precipitate the product. The solid was filtered, washed, and recrystallized from ethanol to afford the corresponding tetrahydrobenzo[b]pyran derivatives in excellent yield.

III. RESULT AND DISCUSSION

Multicomponent reactions (MCRs) efficiently construct complex heterocycles by integrating sequential bond-forming steps in one pot via domino, tandem, or cascade processes [1,25,26,27,39]. Representative examples include V. Ramesh et al.'s five-component domino reaction at 120 °C [1], Sitanshu Kumar et al.'s Knoevenagel-Ugi combination [25], Hong-Jin Lu et al.'s Knoevenagel–cyclocondensation [26], Bhuyan et al.'s microwave-assisted Knoevenagel/aza-Diels–Alder sequence [27], and Heravi et al.'s nanocatalyst- mediated three-component cyclocondensation [39], all highlighting step economy, minimal purification, and efficient scaffold assembly. Reaction conditions range from conventional reflux in ethanol [26] and mild heating at 40 °C [25] to high-temperature domino strategies [1] and rapid microwave-assisted, solvent- and catalyst-free methods [27], with nanocatalysts enabling easy separation and reuse [39]. Green chemistry principles are incorporated through solvent-free protocols [27], eco-friendly solvents [25,26], recyclable catalysts [39], and reduced purification steps [1], minimizing waste and energy consumption. These strategies consistently provide high yields (76-92%) for structurally diverse scaffolds such as coumarin-based α-acyl amino amides [25], spiroindenopyridines [27], tetrahydrobenzo[b]pyrans [39], and multifunctional heterocycles on gram scale [1], while delivering bioactive frameworks with antimicrobial, anti-inflammatory, anticancer, and analgesic activities [1,25,26,27,39], demonstrating the value of MCRs for rapid access to pharmacologically relevant heterocycles in drug discovery and medicinal

IV. CONCLUSIONS

Multicomponent and domino reactions represent efficient and sustainable strategies for the rapid synthesis of biologically relevant heterocycles. The reviewed methodologies demonstrate key advantages such as step economy, high atom efficiency, reduced reaction time, operational simplicity, and minimal purification requirements. Approaches

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including gram-scale domino protocols, sequential Knoevenagel-Ugi reactions, conventional cyclocondensation methods, microwave-assisted solvent-free synthesis, and recyclable nanocatalyst systems collectively highlight the versatility and practicality of one-pot strategies.

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Credit Authorship Contributions Statement
Laxman V. Gavali[1]: Conceptualization, methodology, investigation, writing – original draft.
Raj V. Bhopi[2]: Data curation, formal analysis, validation.
Vishal A. Naik[3]: Supervision, resources, writing – review and editing.
Kajal R. Gaikwad[3]: Conceptualization support, literature survey, writing – review and editing.
Swapnali S. Devkate[2]: Investigation, experimentation, data analysis.
Prathamesh S. Patil[2]: Visualization, manuscript editing, formatting.

Declaration of Competing Interest
The author declares no conflict of interest, financial or personal, that could have influenced the work reported in this paper.

Consent to Publish Declaration
Not applicable.

Ethics and Consent to Participate Declarations
Not applicable.

Data Availability
The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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