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Multicomponent Reactions in the Synthesis of Pharmacologically Active Molecules

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Abstract

Multicomponent reactions (MCRs) have emerged as a transformative approach in modern synthetic organic chemistry, offering highly efficient, atom-economical, and environmentally sustainable pathways for the synthesis of pharmacologically active molecules. These one-pot processes enable the rapid construction of complex molecular architectures by combining three or more starting materials into a single product, significantly reducing reaction steps, waste generation, and purification requirements. Classical MCRs such as the Strecker, Biginelli, and Hantzsch reactions, along with isonitrile-based reactions like the Ugi and Passerini reactions, have been extensively utilized to generate diverse heterocyclic scaffolds with broad therapeutic applications. Recent advancements in MCR strategies, including post-condensation cyclization, diversity-oriented synthesis (DOS), and asymmetric multicomponent reactions (AMCRs), have further expanded their applicability in drug discovery. Moreover, the integration of green chemistry principles, innovative catalytic systems, and modern technologies such as flow chemistry and artificial intelligence has enhanced the efficiency and sustainability of

these processes. MCR-derived compounds have demonstrated significant potential across multiple therapeutic areas, including central nervous system disorders, antimicrobial, antiviral, and cardiovascular diseases. Overall, MCRs represent a powerful platform for accelerating pharmaceutical innovation while aligning with the principles of sustainable chemistry.

1. Introduction

The paradigm of modern synthetic organic chemistry is currently undergoing a decisive transition from traditional linear methodologies to highly convergent and atom-economical strategies (Insuasty et al., 2020). Central to this transformation is the application of multicomponent reactions (MCRs), defined as one-pot processes where three or more starting materials react to form a single product that incorporates most, if not all, of the atoms from the initial reagents (Nadal Rodríguez et al., 2022). This shift is primarily driven by the pharmaceutical industry’s need for increased efficiency, reduced costs, and a smaller environmental footprint. Traditional multi-step synthesis often suffers from low cumulative yields due to successive purification stages and the consumption of vast quantities of solvents, which are increasingly scrutinized under the twelve principles of green chemistry (Anastas & Warner, 1998).

In the context of drug discovery, MCRs represent a powerful tool for navigating chemical space. The concept of bond-forming efficiency (BFE) is essential here, as MCRs allow for the construction of multiple chemical bonds and stereocenters in a single operational step without the isolation of intermediates (Shi et al., 2023). This inherent efficiency addresses the increasing structural complexity of modern active pharmaceutical ingredients (APIs), where conventional linear schemes are often too inefficient in terms of time and waste generation (Wender et al., 2008). By bridging synthetic efficiency with pharmacological relevance, MCRs provide innovative solutions to address emerging therapeutic challenges (Akritopoulou-Zanze, 2008).

The metrics used to evaluate these reactions, such as process mass intensity (PMI) and the E-factor (the ratio of mass of waste to mass of product), favor MCRs over traditional protocols (Constable et al., 2007). In the pharmaceutical sector, the E-factor is historically higher than in other fine chemical industries, often ranging from 25 to 100, due to the high purity requirements and complexity of the molecules (Sheldon, 2007). MCRs significantly lower these values by minimizing sequential multiple reactions and reducing the number of purification stages required (Ruijter et al., 2011). This concept is illustrated in Figure 1, where multiple reactants converge in a single step to form a complex product. The schematic highlights the efficiency and atom economy that distinguish MCRs from traditional linear synthesis.

Figure 1: General Concept of Multicomponent Reactions (MCRs)

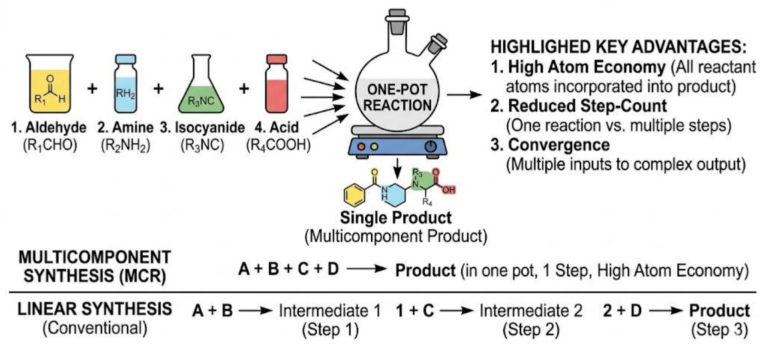


Figure 1: General Concept of Multicomponent Reactions (MCRs)

2. Fundamental Mechanisms of Classical Multicomponent Reactions

The foundation of MCR chemistry rests on several "named" reactions that have been utilized for over a century to construct heterocyclic scaffolds. Understanding the mechanistic pathways of these reactions is critical for their application in target-oriented and diversity-oriented synthesis (Gómez-Biagi & Dicks, 2015).

2.1 The Strecker and Bucherer-Bergs Pathways

The Strecker reaction, the first MCR described in 1850, provides a direct route to alpha-amino nitriles, which are precursors to natural and non-natural amino acids. The mechanism is a sequence of equilibria starting with the acid-promoted condensation of an amine and a carbonyl compound (aldehyde or ketone) to form an iminium ion species, with the concomitant loss of a water molecule (Carvalho et al., 2023). The cyanide nucleophile then attacks the iminium intermediate to give the corresponding alpha-amino nitrile (Eppinger et al., 2022). This process involves a kinetic competition between cyanide and ammonia for the electrophilic carbonyl carbon; however, under the acidic or Lewis acidic conditions typically employed, the iminium pathway predominates (Cores et al., 2022).

The Bucherer-Bergs reaction represents a structural variation that yields hydantoins. Similar to the Strecker reaction, it starts with the formation of an imine from a carbonyl compound and ammonia. This imine receives a cyanide addition, but the resulting alpha-amino nitrile then reacts with CO_2 (usually provided by ammonium carbonate) to form a carbamic acid intermediate (Ganem, 2009). This intermediate undergoes spontaneous cyclization to a 5-iminooxazolidin-2-one, which then undergoes ring opening to an isocyanate and a final cyclization to the hydantoin product. This scaffold is found in several pharmacologically active molecules, including anticonvulsants and mGluR2/3 agonists used in treating schizophrenia (Domling, 2006).

2.2 The Biginelli Reaction and Dihydropyrimidinone Synthesis

Discovered in 1893, the Biginelli reaction involves the three-component condensation of an aldehyde, a beta-ketoester, and urea (or thiourea) to produce 3,4-dihydropyrimidin-2(1H)-ones (DHPMs). The pharmacological importance of the DHPM core cannot be overstated, as it serves as a scaffold for calcium channel blockers, antihypertensives, and anticancer agents (Ugi, 2001).

The mechanism generally proceeds through a Knoevenagel condensation between the urea and the aldehyde to form an iminium intermediate. This is followed by a Michael-type addition of the beta-ketoester and a final cyclocondensation and dehydration step to yield the cyclic DHPM (Trost, 1995). Recent research has focused on enhancing the "greenness" of this reaction using heterogeneous catalysts such as magnetic nanoparticles or bio-derived solvents, and exploring the synthesis of trifluoromethyl-substituted derivatives to enhance biological activity (Rocha et al., 2020).

2.3 The Hantzsch Synthesis of Dihydropyridines

The Hantzsch reaction is the primary MCR for constructing 1,4-dihydropyridines (DHPs), which are vital in managing cardiovascular diseases as calcium channel antagonists. The classical reaction combines an aldehyde, two equivalents of a beta-dicarbonyl compound, and a nitrogen source like ammonium acetate (Ruijter et al., 2018). Modern adaptations have introduced the use of acetaldehyde diethyl acetal as a safer and more stable source of acetaldehyde to facilitate the synthesis of unsymmetrical DHPs, which are otherwise challenging to produce. These DHPs can also serve as precursors to highly substituted pyridines through subsequent aromatization, expanding the available nitrogen heterocycle chemical space (Mohlala et al., 2024).

3. Isonitrile-Based Multicomponent Reactions (IMCRs)

Isonitriles (or isocyanides) are unique in organic chemistry because of the divalent nature of their terminal carbon atom, which possesses both a lone pair and an empty orbital, allowing it to act as both a nucleophile and an electrophile. This dual reactivity makes isonitrile-based multicomponent reactions (IMCRs) exceptionally versatile

(Mohlala & Coyanis, 2024).

3.1 The Ugi Four-Component Reaction (U-4CR)

The Ugi reaction, first reported in 1959, is perhaps the most famous IMCR, involving an aldehyde or ketone, a primary amine, a carboxylic acid, and an isocyanide to produce alpha-acylaminoamides. The reaction is highly exothermic and often yields peptide-like structures known as bis-amides or peptomers, which are classified as peptidomimetics (Al-Shareeda et al., 2021).

The mechanism follows a well-defined sequence:

1. Imine Formation: The amine and carbonyl compound condense to form an imine, with the elimination of water (Chen et al., 2023).
2. Protonation: The carboxylic acid protonates the imine, forming a highly reactive iminium ion (Loh et al., 2018).
3. Nucleophilic Addition: The terminal carbon of the isocyanide adds to the iminium ion to form a nitrilium intermediate (Kornfeind & Fleming, 2024).

The Ugi reaction's high atom economy and procedural simplicity make it a preferred method for creating large compound libraries. It has been instrumental in the synthesis of HIV protease inhibitors like Indinavir (Crixivan) and anesthetics like lidocaine (Lee et al., 2022).

3.2 The Passerini Three-Component Reaction (P-3CR)

The Passerini reaction, discovered in 1921, involves an aldehyde or ketone, a carboxylic acid, and an isocyanide to form alpha-acyloxy carboxamides. In contrast to the Ugi reaction, the Passerini reaction does not involve an amine, and the isocyanide reacts directly with the carbonyl group and carboxylic acid. This reaction is frequently used to synthesize libraries for Alzheimer's disease research, such as chromone-donepezil hybrids (Malek et al., 2019).

4. Advanced Synthetic Strategies and Scaffold Diversity

MCRs are increasingly being combined with secondary cyclization steps to access more complex and rigid scaffolds, a technique often referred to as "MCR-plus" or post-MCR cyclization (Tandi et al., 2025).

4.1 Ugi-Deprotection-Cyclization (UDC) and Post-Condensation

The Ugi adduct itself is a linear bis-amide, but by incorporating bifunctional reagents, it can be transformed into a variety of heterocyclic scaffolds. The Ugi-Deprotection-Cyclization (UDC) procedure involves the use of a protected functional group in one of the Ugi components. Upon deprotection, the newly freed functional group can react with the amide backbone to form cyclic structures such as benzimidazoles, benzodiazepinediones, quinoxalinones, and piperazines (Tripolitsiotis et al., 2020).

Variations of this approach include Ugi-Reduction-Cyclization (URC), where a nitro or azide group is reduced post-Ugi to trigger cyclization, and Ugi-Heck or Ugi-Buchwald-Hartwig combinations with metal-catalyzed cross-coupling (Campos-Prieto et al., 2024).

4.2 Diversity-Oriented Synthesis (DOS) and Chemical Genetics

Diversity-Oriented Synthesis (DOS) aims to synthesize collections of molecules that represent the variety of architectures recognized by nature's biomolecules. MCRs are the concept of choice for DOS because they allow for the simultaneous generation of three types of diversity: appendage, stereochemical, and skeletal diversity (Mandal & Khan, 2024). This is vital for chemical genetics, where small molecules are used to perturb biological systems and identify gene products or pathways (Palanivel & Gnanasambandam, 2020).

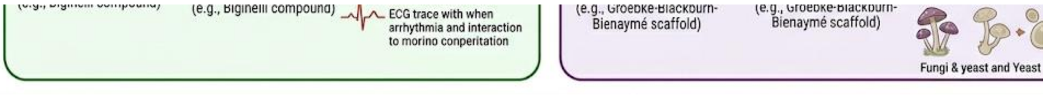
Table 1. Comparison of Target-Oriented Synthesis (TOS) and Diversity-

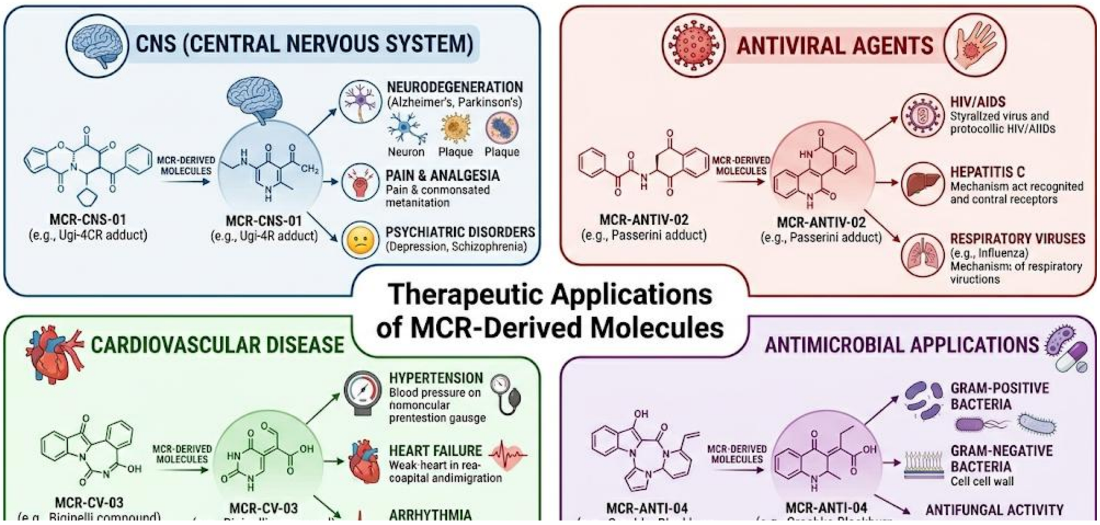
Oriented Synthesis (DOS)

Feature	Target-Oriented Synthesis (TOS)	Diversity-Oriented Synthesis (DOS)
Objective	Single specific target molecule (Rocha et al., 2020)	Structurally diverse compound libraries (Tandi et al., 2025)
Strategy	Retrosynthetic analysis from target (Trabocchi & Schreiber, 2013)	Forward-synthetic exploration of space (Spring, 2013; Trabocchi & Schreiber, 2013)
Main Tool	Sequential linear steps (Rocha et al., 2020)	Multicomponent reactions (Tandi et al., 2025)
Application	Optimization of a known lead (Trabocchi & Schreiber, 2013)	Lead identification/Chemical genetics (Spring, 2013)

5. Pharmacological Landscape of MCR-Derived Molecules

MCRs have been successfully applied across a broad range of therapeutic areas, facilitating the discovery and manufacturing of both small-molecule drugs and clinical candidates (Sakthivel & Singh, 2026). The broad therapeutic relevance of MCR-derived compounds is summarized in Figure 2. It highlights their applications across multiple disease areas.





5.1 CNS Disorders and Multi-Target Directed Ligands (MTDLs)

The multifactorial nature of central nervous system (CNS) pathologies requires drugs capable of binding to multiple enzymatic systems simultaneously. For example, researchers have developed chromone-donepezil hybrids (CDHs) via the Passerini reaction to combine the antioxidant properties of chromones with the cholinesterase inhibitor activity of donepezil (Zięba et al., 2022).

5.2 Antiviral, Antimicrobial, and Antiparasitic Agents

The Neuraminidase inhibitor Oseltamivir (Tamiflu) can be synthesized through an enantioselective multicomponent process involving a sequential Michael addition and cyclization. In antiparasitic research, the synthesis of Praziquantel (PZQ) derivatives has been revolutionized by an Ugi 4-CR followed by a Pictet-Spengler cyclization, allowing for the rapid generation of over 400 analogues to explore structure-activity relationships (Dömling et al., 2012).

5.3 Cardiovascular and Anti-Inflammatory Therapeutics

Dihydropyridines like nifedipine and amlodipine remain the gold standard for treating hypertension, and MCRs like the Hantzsch and Biginelli reactions continue to be used to develop next-generation isosteres (Rocha et al., 2020). In the anti-inflammatory field, quinazolinone derivatives have been synthesized via one-pot MCRs involving isatoic anhydride, triethyl orthoacetate, and aniline derivatives to produce drugs like methaqualone and diproqualone (Zohny et al., 2023).

6. Asymmetric Multicomponent Reactions (AMCRs)

The synthesis of enantiopure compounds is a critical requirement in modern drug development. Asymmetric multicomponent reactions (AMCRs) aim to control multiple stereocenters in a single step, which remains a challenge due to mechanism complexity (Wang et al., 2021).

6.1 Organocatalytic Advancements

Chiral organocatalysts, such as proline and its derivatives, have become essential tools for AMCRs. Proline acts as a privileged catalyst by forming structurally defined enamines with carbonyl compounds. Chiral Brønsted acids, particularly chiral phosphoric acids (CPAs), are widely used in the asymmetric Biginelli and Strecker reactions, with catalysts featuring a TADDOL or BINOL core providing a well-defined asymmetric environment for enantioinduction (Tandi et al., 2025).

6.2 Transition Metal and Photoredox Catalysis

Transition metal catalysts, often in combination with chiral ligands like bisoxazolines (BOX), are used to promote regioselectivity and stereoselectivity in MCRs (Rocha et al., 2020). For example, a photoredox/chromium-catalyzed three-component arylalkylation of 1,3-dienes through C-H functionalization has been reported to yield chiral homoallylic alcohols with excellent enantioselectivity (Chacko & Shivashankar, 2016).

7. Sustainable and Green MCR Methodologies

Green chemistry seeks to minimize the environmental and health impacts of chemical production, and MCRs are a practical strategy to achieve these goals (Mohlala et al., 2024; Tripolitsiotis et al., 2020).

7.1 Innovative Catalytic Systems

The development of recyclable heterogeneous catalysts is a major focus. Magnetic nanoparticle (MNP)-based catalysts can be easily recovered from reaction mixtures using an external magnet, allowing for their reuse in multiple cycles. For example, CS-g-PAN/$Fe3O4$ has been used as a sustainable catalyst for the synthesis of biologically active dihydropyrano[2,3-c]pyrazoles (Mawlid et al., 2024).

7.2 Solvent Innovation and Microwave Assistance

The use of "green" solvents, such as water or Deep Eutectic Solvents (DES), is expanding because they have low vapor pressure and are non-flammable. Microwave irradiation (MI) is also employed to accelerate reaction rates and improve yields compared to traditional reflux methods, providing efficient internal heating and shortened reaction times (Jayant et al., 2025).

8. Technological Frontiers: Flow Chemistry, Automation, and AI

The integration of MCRs with modern technological platforms is significantly accelerating the drug discovery and optimization lifecycle (Sharma et al., 2021).

8.1 Continuous Flow Chemistry and Telescoping

Continuous flow chemistry offers superior control over reaction variables such as temperature and residence time. Reagents are continuously fed into microreactors, facilitating the scaling of lead compounds without re-optimization. The ability to "telescope" multiple steps where the output of an MCR is directly fed into subsequent reaction units enhances efficiency (Menzel et al., 2024).

8.2 AI-Driven Optimization and Robotic Synthesis

The multidimensional space of MCR optimization is now being navigated using Artificial Intelligence (AI) and Machine Learning (ML). Bayesian optimization is a sample-efficient strategy used to find ideal parameters with minimal experimental trials. By 2025, AI is expected to automate patient recruitment for clinical trials and generate hundreds of thousands of potential drug molecules through molecular modeling (Pawar et al., 2025).

9. Comparative Analysis of MCR Efficiency in Drug Discovery

To illustrate the practical advantages of MCRs, it is useful to examine the synthesis of common drugs compared to traditional industrial methods. Lidocaine is a prime candidate for this comparison (Salah, 2025).

Table 2. Efficiency Metrics Comparison for Lidocaine Synthesis

Parameter	Traditional Industrial Route	Ugi 3-Component Reaction
Step Count	Two steps (linear) (Lee et al., 2022)	One step (one-pot) (Lee et al., 2022)
Key Reagents	Corrosive acid chloride, iron/tin/HCl (Lee et al., 2022)	Aldehyde, amine, isocyanide (Lee et al., 2022)
Conditions	Refluxing toluene (110 degrees C) (Lee et al., 2022)	Room temperature in methanol (Lee et al., 2022)
Atom Economy	Lower (waste in each step) (Lee et42 al., 2022)	100% (high atom economy) (Lee et al., 2022)
Process Mass Intensity	High (Lee et al., 2022)	less than 15-60% of traditional routes (Lee et al., 2022)
Purification	Multiple extractions/distillation (Lee et al., 2022)	Simple precipitation and filtration (Lee et al., 2022)

This comparison highlights how MCRs satisfy "Ideal Synthesis" criteria by providing single-step reactions in green solvents with high yield (Lee et al., 2022).

10. Structural Complexity: Macrocycles and Atropisomers

The application of MCRs has expanded beyond simple heterocycles to include macrocycles and molecules with axial chirality, significant for difficult genomic targets (Roper et al., 2025).

10.1 Multicomponent Macrocyclization

Macrocycles are highly underrepresented in screening libraries due to the challenges of ring closure. MCRs offer a convergent and fast strategy for macrocyclization involving the nucleophilic ring opening of cyclic carboxylic acid anhydrides with diamines followed by an Ugi ring closure. This method allows for the rapid assembly of structurally diverse artificial macrocycles (Dömling et al., 2012).

10.2 Atropisomeric Peptide Analogues

Atropisomers are molecules that possess axial chirality due to restricted rotation. Recently, a 4-component Ugi reaction was described for the stereoselective synthesis of novel atropisomeric peptide analogues using ortho-substituted anilines and isocyanides, accessing complex products possessing both central and axial chirality in high yield and excellent diastereoselectivity (greater than 95:5 d.r.) (Nadal Rodríguez et al., 2022).

11. Future Perspectives and Industry Integration

The objective of an "ideal synthesis" is to generate molecular complexity in minimal steps with minimal waste (Ruijter et al., 2018). Future developments are likely to focus on asymmetric radical-polar crossover utilizing photoredox catalysis and self-optimizing robotic platforms that can perform synthesis and analysis without human input (Constable et al., 2007).

12. Conclusions

Multicomponent reactions have revolutionized the synthesis of pharmacologically active molecules by providing efficient, versatile, and sustainable alternatives to traditional multi-step synthetic routes. Their ability to generate structurally complex and diverse compounds in a single operational step significantly enhances synthetic efficiency while reducing environmental impact. Classical and isonitrile-based MCRs continue to play a central role in constructing biologically relevant scaffolds, while advanced methodologies such as post-MCR cyclization, asymmetric catalysis, and diversity-oriented synthesis further expand chemical space and therapeutic potential. The incorporation of green chemistry principles, recyclable catalysts, and emerging technologies like flow chemistry and artificial intelligence is expected to further optimize MCR processes and accelerate drug discovery pipelines. Despite ongoing challenges, particularly in stereocontrol and mechanistic complexity, MCRs remain a cornerstone of modern medicinal chemistry. Future developments will likely focus on automation, sustainable practices, and innovative catalytic systems, solidifying MCRs as indispensable tools in the design and synthesis of next-generation pharmaceuticals.

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