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Multicomponent Reactions in the Synthesis of Biologically Active Heterocycles: A Comprehensive Review

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Abstract

Multicomponent reactions (MCRs) have become an indispensable instrument in modern synthetic chemistry, mainly because they allow several covalent bonds, and a non-trivial amount of molecular complexity, to be assembled within a single operation. Heterocyclic compounds, which underpin the structural skeleton of roughly two thirds of the small-molecule drugs in clinical use, are particularly well served by such transformations. The aim of this review is to gather, from a wide pool of literature, the most important MCR-based approaches that lead to biologically active nitrogen-, oxygen- and sulfur-containing heterocycles. We start with a short historical and mechanistic background of the classical "named" multicomponent reactions – Strecker, Hantzsch, Biginelli, Passerini and Ugi – and then move to the rapidly expanding catalytic and green variants developed during the last two decades. The discussion is organised around the heterocyclic core that is produced (dihydropyrimidinones, 1,4-dihydropyridines, imidazoles, pyrroles, quinolines, pyrazoles, indoles, thiazolidinones and 4H-chromenes), and, in each case, we connect the synthetic route to its principal pharmacological context: anticancer, antimicrobial, antimalarial, anti-inflammatory and cardiovascular activity. Particular attention is given to recent strategies that employ water, deep eutectic solvents, magnetic nanocatalysts, microwave irradiation and ultrasonic activation. Five figures and one summary table illustrate the discussion. The review closes with a critical comment on current challenges, including the still-modest diastereoselectivity of many three-component routes, scope limitations of certain reagent combinations, and the unavoidable trade-off between sustainability and process robustness.

Keywords: *Multicomponent Reactions; Heterocycles; Biginelli; Hantzsch; Ugi; Bioactive Molecules; Green Chemistry.*

I. INTRODUCTION

The push towards economical, atom-efficient and step-economical synthesis has, in many respects, reshaped how organic chemists think about a target compound. Where the older retrosynthetic mindset typically partitions a molecule into a chain of two-component disconnections, multicomponent chemistry collapses that same logic into a much smaller number of operations. A multicomponent reaction (MCR), in its most common definition, is a transformation in which three or more reagents combine in one pot – ordinarily without the isolation of any intermediate – to deliver a single product that incorporates atoms or fragments from all of the partners [1,2]. The appeal of such transformations is rather straightforward: fewer purification steps, less solvent, less waste, and direct access to libraries of densely functionalised compounds with the kind of complexity that is otherwise hard to assemble.

Heterocyclic frameworks have always been an obvious target for MCR chemistry. Hundreds of natural products and a very large fraction of the FDA-approved pharmacopoeia contain at least one heterocyclic ring; recent surveys place the figure at around 60–75% of small-molecule drugs [3,4]. Nitrogen-containing heterocycles, in particular, dominate, and they are responsible for many crucial pharmacological properties – hydrogen-bond donor/acceptor profiles, basicity, conformational rigidity, and π–π interactions with biological targets. Whether one looks at a kinase inhibitor, an angiotensin-receptor blocker, an antimalarial quinoline or a non-nucleoside antiviral agent, the underlying scaffold is more often than not heterocyclic in nature.

It is therefore not surprising that the MCR toolbox has been progressively refined to deliver these scaffolds with greater scope and selectivity. Historically the field was launched by Strecker's 1850 synthesis of α-

aminonitriles from an aldehyde, ammonia and hydrogen cyanide [5], followed not long after by Hantzsch's 1,4-dihydropyridine synthesis (1881) [6], the Biginelli reaction (1893) [7], the Mannich condensation (1912), and, well into the twentieth century, by the isocyanide-based reactions of Passerini (1921) and Ugi (1959) [8,9]. These early reactions still constitute the conceptual backbone of MCR research today. What has changed, sometimes dramatically, is how they are carried out: Lewis acid catalysis, Brønsted acid catalysis, transition-metal catalysis, organocatalysis and, more recently, nanocatalysis have all extended the scope of these reactions to substrates that previously gave only modest results. Parallel to that, green chemistry tools – water, ionic liquids, deep eutectic solvents, microwave heating, ultrasound – have made the reactions a lot more attractive from an environmental standpoint.

The purpose of this comprehensive review is to give a current, accessible overview of how MCRs continue to be used in the synthesis of biologically relevant heterocycles. It is structured around three pillars: (i) the classical reactions and their mechanisms; (ii) the catalytic and green improvements that have transformed them into useful library-generating tools; and (iii) the bioactive scaffolds they generate, with a focused commentary on the pharmacological role of each ring system. We have tried to keep the discussion practical rather than exhaustive, and to point out, where relevant, the methodological caveats that often go unmentioned in primary papers.

II. CLASSICAL MULTICOMPONENT REACTIONS

The earliest MCRs were, almost without exception, discovered by accident, but their mechanistic underpinnings are now reasonably well understood and remarkably similar across the different cases. In nearly all of them the reaction starts with an electrophilic condensation between two of the partners – most often an aldehyde with an amine, or an aldehyde with a 1,3-dicarbonyl – to form an in-situ intermediate (an imine, enamine or N-acyliminium ion) that is then captured by the third partner. The four most influential representatives are summarised in Figure 1.

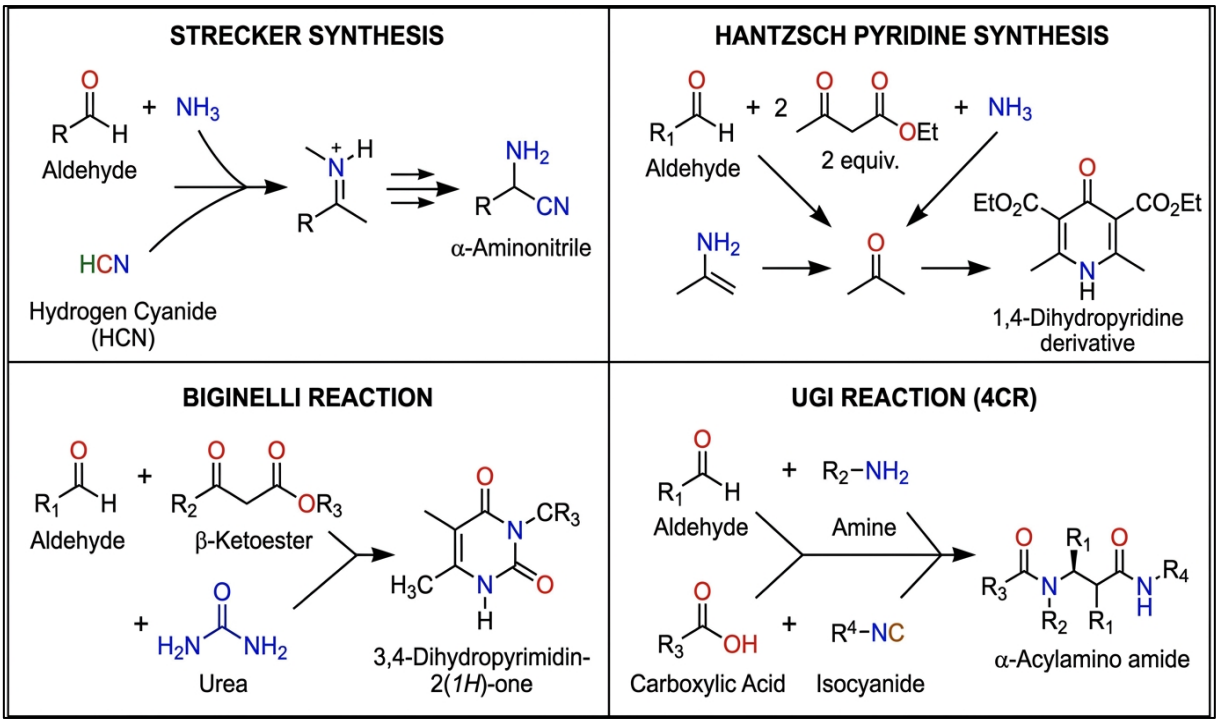

Fig 1 Overview of Four Cornerstone Multicomponent Reactions – Strecker, Hantzsch, Biginelli and Ugi – Showing the Principal Reactants Converging Onto the Heterocyclic or Amide-Rich Product in a Single Operation.

The Strecker reaction is perhaps the simplest case. An aldehyde reacts with ammonia to form an imine, and HCN (or a cyanide salt) adds to give an α-aminonitrile, which on hydrolysis affords an α-amino acid. Although the Strecker reaction is not, strictly speaking, a heterocycle synthesis, the α-aminonitrile intermediate is a convenient handle for further annulations into imidazolines, tetrazoles and other azaheterocycles.

The Hantzsch dihydropyridine synthesis [6] is more directly relevant. Combination of an aldehyde, two equivalents of a β-ketoester and ammonia (or an ammonium salt) yields a symmetrical 1,4-dihydropyridine (1,4-DHP). The accepted mechanism passes through (i) a Knoevenagel-type condensation between the aldehyde and one of the β-ketoester molecules; (ii) enamine formation between the second β-ketoester and ammonia; (iii) Michael-type addition of the enamine to the Knoevenagel adduct; and (iv) cyclodehydration. The Hantzsch product is the direct parent of the dihydropyridine class of calcium channel blockers – Nifedipine, Amlodipine and Felodipine – one of the great success stories in MCR chemistry.

The Biginelli reaction, reported in 1893, is conceptually similar to the Hantzsch synthesis but uses urea (or thiourea) in place of ammonia, which inserts an

additional ring nitrogen into the product [7]. An aldehyde, a β-ketoester and urea condense in the presence of an acid catalyst to give a 3,4-dihydropyrimidin-2(1H)-one (DHPM). The mechanism (Figure 2) was the subject of some debate before NMR experiments and DFT studies by Kappe and others firmly established the N-acyliminium pathway as the dominant route [10]. The reaction has attracted unusual attention because the DHPM core shows calcium-channel modulation, antiviral, antibacterial and antitumour activity. Monastrol – a Biginelli product – was the first small-molecule inhibitor of the mitotic kinesin Eg5, and that single observation triggered an entire wave of medicinal interest in the scaffold [11].

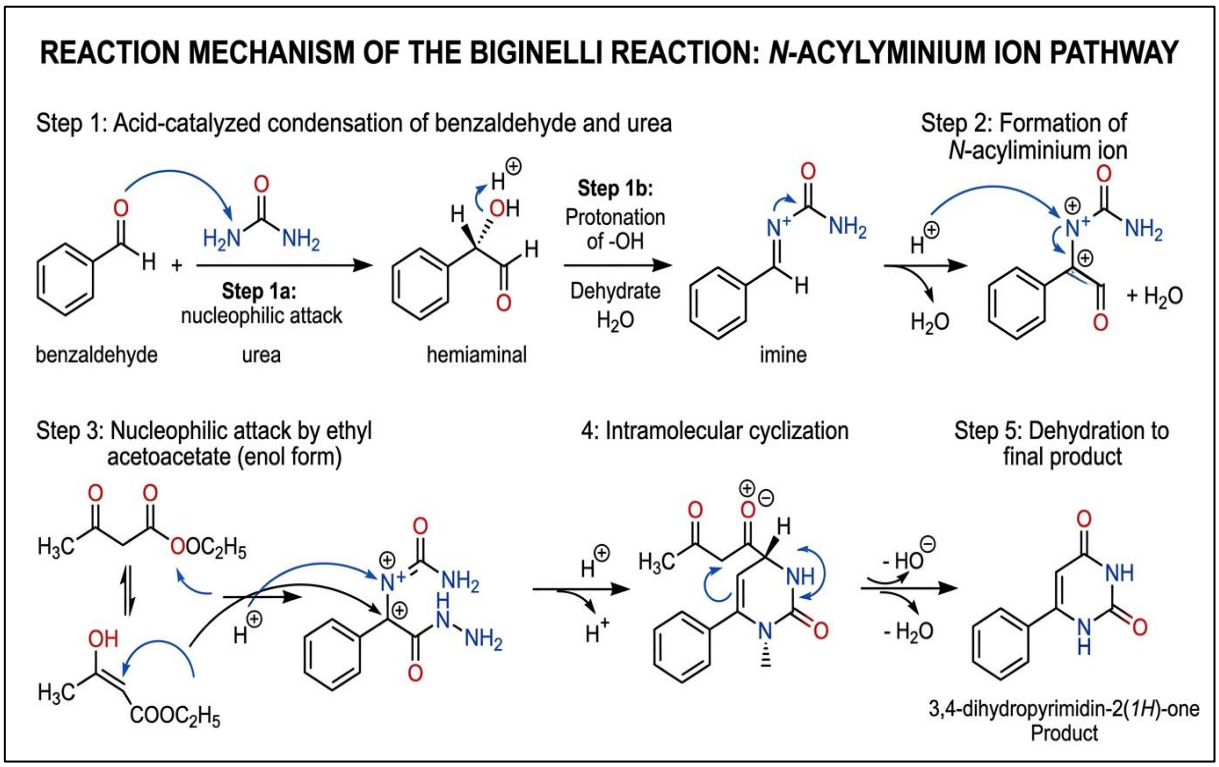

Fig 2 Accepted Iminium Pathway of the Biginelli Reaction. Acid-Catalysed Condensation of Benzaldehyde with Urea Generates an N-Acyliminium ion that is Trapped by the Enol form of Ethyl Acetoacetate; Subsequent Intramolecular Cyclisation and Dehydration Deliver the 3,4-Dihydropyrimidin-2(1H)-One Product.

The Passerini three-component reaction (P-3CR), discovered in 1921, joins a carboxylic acid, an aldehyde (or ketone) and an isocyanide to give an α-acyloxy amide. It is unusual in that it does not require any catalyst; the isocyanide acts both as a nucleophile and as an electrophile, inserting between the acid and the carbonyl. The richer Ugi four-component reaction (U-4CR) [8,9] adds an amine into the mix, so that the acyloxy product is replaced by an α-acylamino amide. Ugi-type chemistry, in turn, is the basis of an enormous body of post-condensation cyclisations that deliver indoles, benzodiazepines, tetrazoles, oxazoles, ketopiperazines and many other heterocyclic systems. The structural diversity that can be reached from Ugi/Passerini chemistry is, in fact, one of the main reasons MCRs gained such traction in combinatorial and parallel synthesis during the 1990s and early 2000s.

What runs through all four reactions is essentially the same idea: a small set of cheap building blocks is converted, in a single operation, into a molecule that would otherwise require multiple linear steps. The atom economy is typically very high – frequently above 80%, with water as the only by-product – and step economy is, more or less by definition, optimal.

III. CATALYSIS AND ENABLING TECHNIQUES

For all the elegance of the classical conditions, they have practical limitations. Many of the original protocols rely on stoichiometric mineral acids (HCl, H2SO4), give moderate yields with sterically demanding aldehydes, and produce viscous mixtures that complicate work-up. The development of more refined catalytic systems was therefore inevitable. Figure 4 sketches the main families of green-and-clean strategies that have been deployed during the past twenty-five years.

Lewis acid catalysis has been widely used in Biginelli, Hantzsch and Mannich variants. Classical homogeneous activators such as FeCl3, BF3·OEt2, Yb(OTf)3, La(OTf)3, In(OTf)3, ZnCl2 and CeCl3 all work, although the lanthanide triflates are the most appreciated for their water tolerance and high turnover [12,13]. Yields of DHPMs routinely exceed 85–90% under these conditions, and chemoselectivity is markedly improved for ortho-substituted or electron-rich aromatic aldehydes that historically gave the most trouble.

Brønsted acid catalysis – both with strong simple acids such as p-toluenesulfonic acid (PTSA) and with the chiral phosphoric acids (CPAs) of the BINOL family – has

opened the door to enantioselective MCRs. Akiyama and Terada's pioneering work on chiral phosphoric acids in the early 2000s [14] set the stage for asymmetric Biginelli, Mannich and aza-Friedel–Crafts variants. Enantiomeric excesses above 90% are now commonly reported, although catalyst loading and substrate scope remain practical constraints.

Heterogeneous catalysts have, arguably, had the largest practical impact. Zeolites, silica-supported sulfonic acids, montmorillonite K10, mesoporous metal oxides, and magnetically separable Fe3O4-based nanocomposites – such as Fe3O4@SiO2–SO3H, Fe3O4@MIL-101 and CoFe2O4 nanoparticles – have all been used for Biginelli, Hantzsch and Groebke–Blackburn–Bienaymé reactions. The really compelling feature is reusability: many of these catalysts can be recovered with a simple magnet, washed and recycled for five to ten consecutive runs without significant loss of activity [15,16].

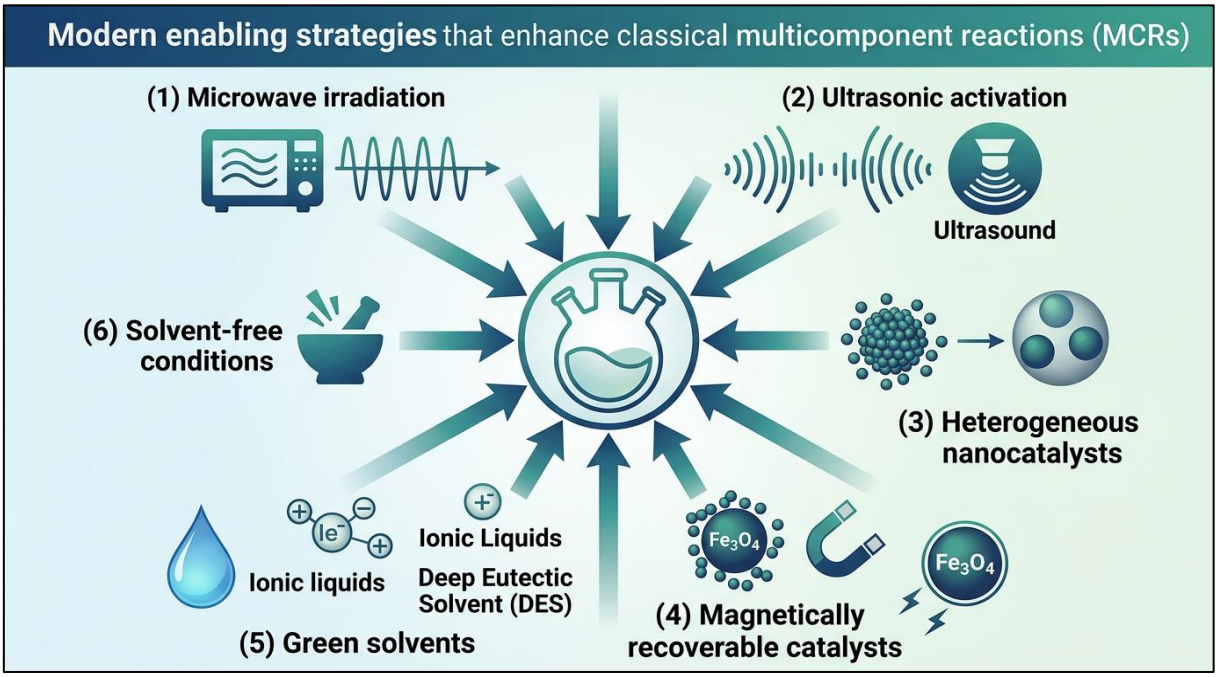

Fig 3 Modern Enabling Strategies that Have Refined the Classical MCRs. Microwave and Ultrasonic Activation, Heterogeneous and Magnetically Recoverable Nanocatalysts, Aqueous Media, Ionic Liquids/Deep Eutectic Solvents, and Solvent-Free Protocols Converge on the same Multicomponent Vessel to Cut Time, Energy and Waste While Extending the Scope of these Reactions.

Non-thermal activation has also become routine. Microwave irradiation cuts reaction times dramatically (often from hours to minutes) and tends to suppress side products by avoiding hot spots and reflux artefacts. Several Biginelli protocols that need 8–12 hours under conventional heating reach over 90% conversion within 5–15 minutes under microwave conditions [17]. Ultrasound, with its cavitation-driven micro-mixing, has likewise improved yields and lowered catalyst loadings in several DHP and pyrrole syntheses. Solvent-free protocols, where the reactants are simply ground together (sometimes with a small amount of solid acid), align with the principles of green chemistry and remove the solvent disposal step entirely. Water and ethanol have replaced more aggressive solvents in many published procedures; water in particular has the additional benefit that the hydrophobic effect can accelerate the reaction.

Nanocatalysis deserves a separate mention. Metal-organic frameworks (MOFs), carbon dots, palladium nanoparticles immobilised on graphitic carbon nitride, and silver or gold nanoparticles supported on a variety of carriers have all been deployed in MCRs leading to bioactive heterocycles [18,19]. Yields are typically as good as, or better than, those obtained with molecular catalysts; the available surface area per mole is enormous, and the catalysts are usually recyclable. The main drawback is reproducibility – small differences in nanoparticle size, capping ligand and support can have outsized effects on activity, and a procedure that performs beautifully in one laboratory occasionally translates poorly to another.

IV. HETEROCYCLIC SCAFFOLDS AND THEIR BIOLOGICAL ACTIVITY

The remainder of this review surveys the most important heterocyclic systems that are accessible by MCR chemistry and that have an established biological profile. Figure 4 displays a representative gallery of nine scaffolds together with prototypical drug examples; Table 1 summarises typical synthetic conditions and biological activities; and Figure 5 maps the major therapeutic classes onto the corresponding ring systems.

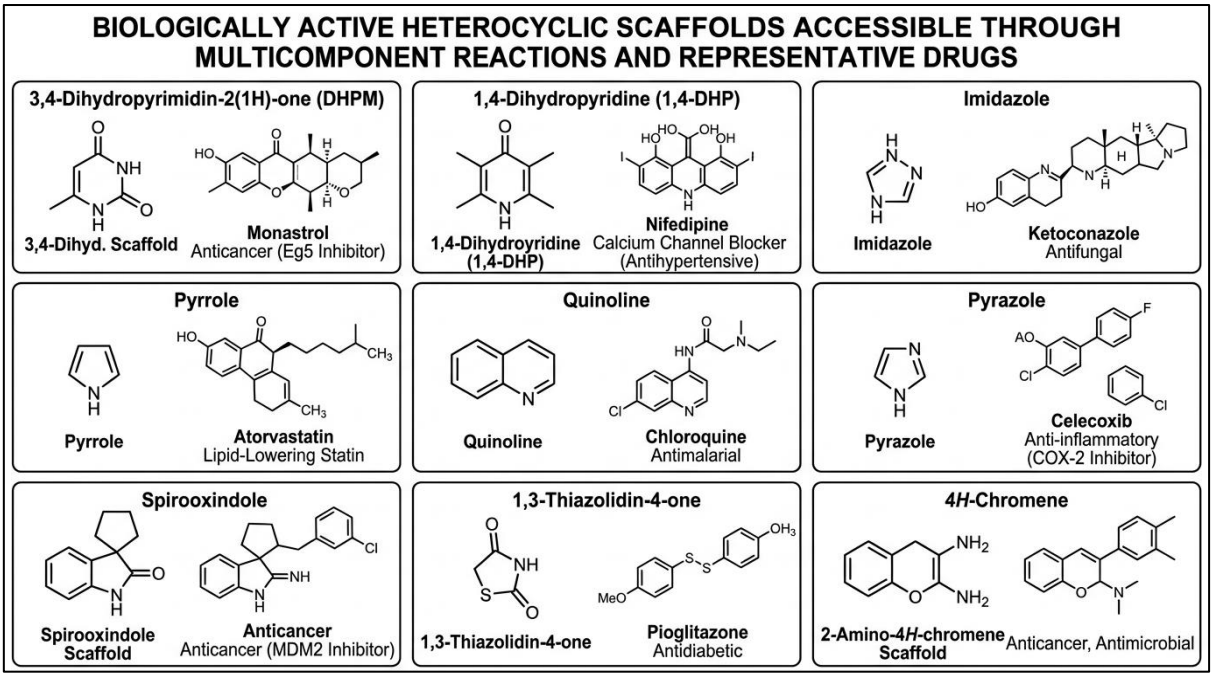

Fig 4 Gallery of Nine Biologically Active Heterocyclic Scaffolds that are Commonly Accessible Through Multicomponent Reactions, Each Shown with a Prototypical Drug or Lead Compound and its Main Therapeutic Indication.

➢ *Dihydropyrimidinones (DHPMs)*

As outlined earlier, DHPMs are the canonical Biginelli products. Beyond the calcium-channel-modulating activity that initially attracted medicinal chemists, DHPMs have shown anticancer activity through inhibition of the mitotic kinesin Eg5, antiviral activity against HIV and HCV, and antibacterial activity against both Gram-positive and Gram-negative strains [11,20]. The aryl substituent at C-4 is the principal handle for tuning activity; electron-withdrawing groups (–NO2, –Cl, –CF3) frequently increase potency in the anticancer setting, while electron-donating groups at the same position tend to favour the antihypertensive profile.

➢ *1,4-Dihydropyridines (1,4-DHPs)*

Hantzsch's reaction remains the most direct entry into the 1,4-DHP scaffold. Nifedipine – the prototypical agent – was the first 1,4-DHP calcium-channel blocker introduced clinically (in 1975) and is still on the WHO Essential Medicines list. Subsequent derivatives (Amlodipine, Felodipine, Nicardipine, Lacidipine) improved selectivity for vascular over cardiac calcium channels. More recent work has uncovered antitumour, antitubercular, anti-Alzheimer and antioxidant activity for structurally diverse 1,4-DHPs [21], which underscores the persistent value of the Hantzsch ester not only as a target but also as a versatile hydride source in modern transfer-hydrogenation chemistry.

➢ *Imidazoles*

Several MCR variants produce imidazoles. The four-component condensation of a 1,2-diketone, an aldehyde, an amine and ammonium acetate – sometimes called the Debus–Radziszewski reaction, although it is also referred to as the Davidson protocol – gives 1,2,4,5-tetrasubstituted imidazoles in a single step [22]. The imidazole nucleus appears in some of the most widely used antifungals (Ketoconazole, Clotrimazole, Miconazole), antiprotozoals (Metronidazole, Tinidazole), antihypertensives (Losartan), anticancer agents (Dacarbazine) and proton-pump inhibitors. Bioactivity-driven SAR studies on MCR-synthesised imidazoles have, somewhat consistently, identified the importance of the C-2 aryl group and the N-1 substituent for binding to fungal cytochrome P-450 or to bacterial nitroreductases.

➢ *Pyrroles*

Several MCR routes – including modern modifications of the Paal–Knorr reaction and isocyanide-based protocols of the van Leusen type – provide substituted pyrroles. Perhaps the best-known example is the atorvastatin (Lipitor) framework, in which the central pyrrole ring carries a fluorophenyl group and a pendant β,δ-dihydroxy acid chain that is essential for HMG-CoA reductase inhibition. Beyond the statin class, pyrrole-containing natural products such as lamellarins and prodigiosins show striking antitumour activity, and synthetic pyrroles have been developed as antibacterial, antifungal and tubulin-binding agents [23].

➢ *Quinolines*

The Friedländer, Doebner–Miller and Combes reactions are the historical entries to quinoline chemistry. More recent MCR variants combine an aniline, an aldehyde and a 1,3-dicarbonyl (or an alkyne) to give substituted quinolines or quinolinones in one pot, frequently with Lewis acid or solid acid catalysis. Quinoline is one of the oldest pharmacophores: Chloroquine, Primaquine, Mefloquine and Hydroxychloroquine are still mainstays of antimalarial chemotherapy. Quinoline derivatives are also active as antibacterial, antitubercular, antifungal and anticancer agents [24]; the topoisomerase II inhibition shown by Camptothecin (a quinoline alkaloid) is mechanistically distinct and clinically valuable.

➢ *Pyrazoles*

MCRs of hydrazines with β-ketoesters and aldehydes give 3,4,5-trisubstituted pyrazoles, while the use of malononitrile or arylidene malononitriles affords pyranopyrazoles and other fused systems. Celecoxib – a 1,5-diarylpyrazole bearing a sulfonamide group – is the canonical example of a clinically used anti-inflammatory drug carrying this nucleus, and many other COX-2 selective inhibitors share the same core [25]. Pyrazole derivatives have also been described as kinase inhibitors, CB1 cannabinoid antagonists (Rimonabant) and antibacterial agents.

➢ *Indoles*

Indole-based MCRs are particularly diverse. The Mannich-type reaction of indoles with aldehydes and amines gives 3-aminomethyl indoles, while three-component reactions involving indole, isatin and a 1,3-dicarbonyl produce spirooxindoles. Spirooxindoles, in particular, have received enormous attention as MDM2–p53 disruptors with anticancer potential [26]. The plant alkaloid family is, of course, replete with indole pharmacophores (vincristine, vinblastine, reserpine, strychnine), and many of those frameworks have inspired entirely new MCR designs.

➢ *Thiazolidinones and Thiazoles*

Three-component condensation of an aldehyde, a primary amine and mercaptoacetic acid gives 1,3-thiazolidin-4-ones, while the Hantzsch thiazole synthesis (an α-haloketone with a thioamide) provides thiazoles. Both classes have been extensively developed as antidiabetics (the glitazones – Pioglitazone and Rosiglitazone), antimicrobials, antivirals and inhibitors of aldose reductase [27].

➢ *4H-Chromenes and Pyranopyrazoles*

Three- or four-component reactions between an aromatic aldehyde, malononitrile and a phenol (or a 1,3-dicarbonyl) give 4H-chromenes – abundant antiproliferative pharmacophores – and pyranopyrazoles, with reported antitumour, anticoagulant and antifungal activities [28]. Both scaffolds are readily synthesised in water or in a deep eutectic solvent, often with no catalyst beyond a small amount of base.

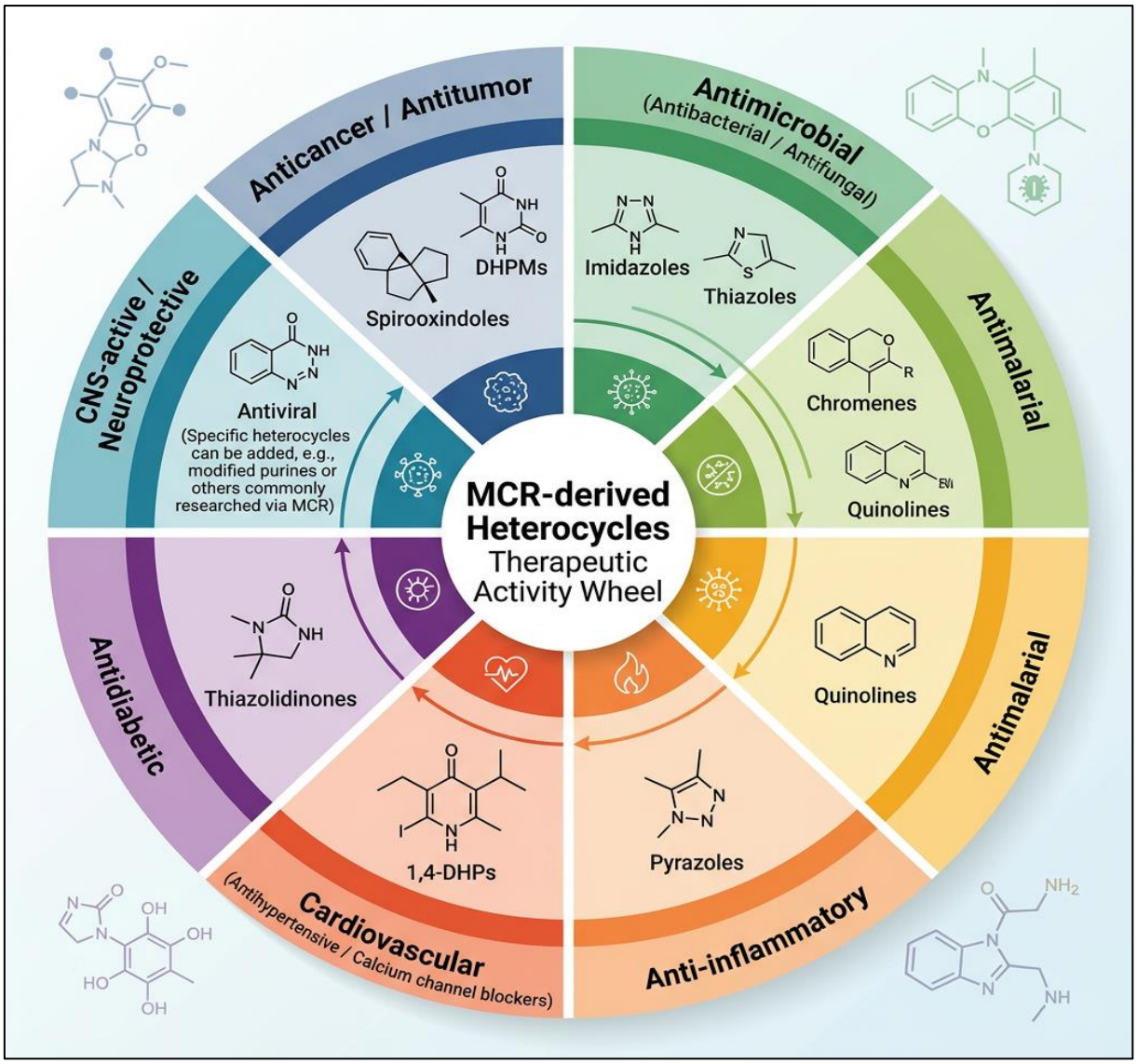

Fig 5 Therapeutic Activity "Wheel" Showing how MCR-Derived Heterocycles Populate Every Major Pharmacological Category, from Anticancer and Antimicrobial Agents to Cardiovascular, Antidiabetic and Anti-Inflammatory Drugs.

Table 1 Representative MCR-Based Syntheses of Biologically Active Heterocycles, with Typical Components, Catalysts, Yield Ranges and Principal Pharmacological Profiles.

Heterocyclic scaffold	Typical MCR	Components	Common catalyst	Yield (%)	Reported bioactivity
3,4-Dihydropyrimidin-2(1H)-one	Biginelli	Aldehyde + β-ketoester + urea/thiourea	PTSA, Yb(OTf)3, Fe3O4@SiO2–SO3H	70–95	Anticancer (Eg5 inhibition), antihypertensive, antiviral
1,4-Dihydropyridine	Hantzsch	Aldehyde + 2 × β-ketoester + NH4OAc	I2, CeCl3, ZnO nanoparticles	65–92	Ca2+-channel blockers, antitubercular, antioxidant
1,2,4,5-Tetrasubstituted imidazole	Debus–Radziszewski	1,2-Diketone + aldehyde + amine + NH4OAc	AcOH, ZrOCl2, MgFe2O4	75–96	Antifungal, antiprotozoal, AT1-antagonist
2,3,5-Trisubstituted pyrrole	van Leusen / Knorr-type	Amine + 1,3-dicarbonyl + nitroalkene (or TosMIC)	l-Proline, K2CO3, ionic liquids	60–88	Anticancer, lipid-lowering (statin core)
Quinoline	Friedländer / Doebner	Aniline + aldehyde + ketone (or alkyne)	p-TsOH, Sc(OTf)3	55–90	Antimalarial, antibacterial, antitubercular
1H-Pyrazole	Knorr-type three-component	Hydrazine + β-ketoester + aldehyde	AcOH, Cu(OTf)2	70–93	Anti-inflammatory (COX-2), antibacterial
2-Amino-4H-chromene	Knoevenagel–Michael cascade	Aldehyde + malononitrile + phenol/dimedone	DBU, β-cyclodextrin, DESs	78–96	Antitumour, antimicrobial
Spirooxindole	1,3-Dipolar 3-component	Isatin + α-amino acid + dipolarophile	None / mild base	60–90	Anticancer (MDM2–p53 disruption)
1,3-Thiazolidin-4-one	Hetero-Mannich	Aldehyde + amine + mercaptoacetic acid	ZnCl2, ionic liquid	65–88	Antidiabetic, antitubercular, antiviral

Across these scaffolds two recurring observations emerge. First, the MCR chemistry typically delivers the heterocycle with high atom economy and low waste, but the surrounding structure–activity space is, in most cases, vast and only sparsely explored. Second, the most productive medicinal-chemistry programmes have invariably coupled MCR-based library synthesis with later stages of focused diversification (typically Suzuki–Miyaura coupling, amide formation or N-alkylation), which suggests that MCRs are most useful as an enabling first step rather than as the sole synthetic strategy.

V. RECENT TRENDS AND CHALLENGES

Over the past decade, three trends have emerged with particular clarity. First, asymmetric MCRs have moved from a niche pursuit to a mature area, especially through the use of chiral phosphoric acids, chiral squaramides and chiral Brønsted bases. Enantiomeric excesses above 90% are now routinely reported in Biginelli, Mannich and Hantzsch chemistries, but the substrate scope is still narrower than for the racemic counterparts, and the catalysts are expensive.

Second, flow chemistry has begun to be applied to MCRs at the gram-to-kilogram scale. Continuous-flow Biginelli, Ugi and Passerini reactions in microreactors offer better heat transfer, finer control over residence time, and a much easier path to scale-up than batch processing. This becomes particularly relevant for processes that require strict thermal control or that involve hazardous reagents (HCN in Strecker, alkyl isocyanides in Ugi).

Third, biocatalysis is starting to make some inroads into MCR chemistry, with imine reductases, transaminases and lipases mediating either the key bond-forming step or the post-condensation modification. This remains an embryonic field; however, the high enantioselectivity and the benign conditions of enzymes are an obvious match for the MCR philosophy.

Several challenges, however, persist. Diastereoselectivity is often poor when more than one stereogenic centre is generated; the products are usually obtained as cis/trans mixtures that must be separated chromatographically. Substrate scope, while wide, has well-known blind spots – heteroaromatic aldehydes (furfurals, pyrrole carbaldehydes), sterically encumbered ketones and aliphatic isocyanides often perform poorly. Catalyst recyclability, though promising on paper for heterogeneous systems, is seldom tested beyond five cycles, and metal leaching from supported catalysts remains a concern from both an environmental and a pharmaceutical standpoint. Finally, scaling several of the

most appealing nanocatalysed MCRs from the academic milligram scale to the multigram scale used in medicinal-chemistry programmes has not always been straightforward.

VI. CONCLUSIONS AND OUTLOOK

Multicomponent reactions are no longer a curiosity of nineteenth-century chemistry; they sit at the heart of modern heterocyclic and medicinal chemistry. By compressing several bond-forming events into a single operation, MCRs deliver complex, biologically relevant scaffolds with a small fraction of the time, solvent and waste of the conventional linear approach. The classical Strecker, Hantzsch, Biginelli, Passerini and Ugi reactions remain conceptual benchmarks, but the field has been transformed by a continuous stream of catalytic and enabling improvements – chiral Brønsted acids, magnetically recoverable nanocatalysts, microwave and ultrasonic activation, water and deep eutectic solvents, and, most recently, continuous-flow and biocatalytic platforms.

Equally important, the bioactive scaffolds delivered by MCRs span essentially the whole pharmacopoeia: cardiovascular (1,4-DHPs), antimalarial (quinolines), anti-inflammatory (pyrazoles), antifungal and antibacterial (imidazoles, thiazoles), antiproliferative (DHPMs, spirooxindoles, chromenes), lipid-lowering (the atorvastatin pyrrole), antidiabetic (thiazolidinediones), and CNS-active (pyridines, benzimidazoles). The challenge for the next decade is not so much to discover new ring systems as to make the existing reactions more selective, more general and easier to scale.

Looking forward, the convergence of MCR chemistry with computational design, machine-learning–guided reaction optimisation and high-throughput screening seems likely to produce step changes in both efficiency and the diversity of accessible scaffolds. In parallel, the growing emphasis on sustainability – embodied in measures such as process mass intensity, E-factor and total energy consumption – will continue to push MCR practitioners towards greener catalysts and benign solvent systems. For students entering the field, and for medicinal chemists hunting for fresh scaffolds, MCRs remain one of the most rewarding starting points in modern organic synthesis.

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