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Chemistry strategies in early drug discovery: an overview of recent trends

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In the scenario of a continuous request for better drugs in shorter times, medicinal chemists must face the challenging task of preparing new patentable molecules, combining high activity and selectivity, drug-likeness and good pharmacokinetic properties. Multiparametric optimization requires a substantial improvement of the efficacy and throughput of the early discovery process, leading to a significant revolution in organic synthesis and chemistry technologies. Chemists are searching for ways to simplify synthetic protocols, for example, by the use of polymer-assisted solution-phase synthesis, microwave-assisted organic synthesis and flow chemistry. Organic synthesis is benefiting of fast and robust reactions, with breakthrough approaches often entailing the privileged use of multicomponent reactions, click chemistry and ring-closing metathesis.

Introduction

Currently, the fundamental issue in the drug discovery process is the high failure rate in clinical trials, mainly due to liabilities related to poor pharmacokinetics, poor efficacy and high toxicity. In order to overcome this problem and avoid failure at a later stage of the process, in recent years a multiparametric approach has found wide application in drug discovery. The determination of activity and selectivity is performed at an early stage of the discovery process, simultaneously with the evaluation of pharmacokinetic and toxicity properties, in order to allow the early selection of the compounds with the best overall balanced drug-like profile.

This strategy required an increase in the throughput of medicinal chemistry in the early drug discovery process, not so much in terms of numbers of compounds, but more with the synthesis of novel, complex and decorated scaffolds.

Consequently, a significant and substantial revolution in chemical technologies and also in organic synthesis is taking place. Even if a complete review of each topic is not possible in this paper, we would like to discuss recent trends and approaches that have brought the most significant improvements in discovery chemistry.

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Technologies

In recent years, organic synthesis has been deeply affected by the introduction of new technologies. Among the most significant technical improvements, the greatest impact has been obtained by polymer-assisted solution-phase synthesis (PASPS), microwave-assisted organic synthesis (MAOS) and, more recently, also by continuous-flow processes.

Polymer-assisted solution-phase synthesis

Solid-supported reagents and scavengers have been widely employed in organic chemistry during recent years in research chemistry, since they allow the simplification of both synthetic procedures and isolation or purification steps, avoiding at the same time the limitations of solid-phase synthesis [1]. The most significant improvement, when PASPS is compared to classical synthesis, is that work-up operations are considerably simplified and reduced to simple filtration. The use of a large excess of reagents (often necessary to drive reactions to completion) is then possible without requiring additional purification steps. Toxic, noxious or hazardous reagents and their by-products can be immobilized and, therefore, not released into the solution thereby improving their general acceptability and safety profile. Owing to site isolation of reagents on the resin bead, species that are incompatible in the solution may be used together to achieve one-pot

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transformations that are not possible under classical homogeneous conditions.

The main drawback is represented by the lower reactivity of the supported reagents when compared to their homogeneous counterparts (due to the kinetic limit of diffusion of the solution species into the solid support): these materials are then usually employed in large excess, thus resulting in higher costs, particularly when considering reaction scale-up.

Almost every kind of organic reaction described in homogeneous solution can be performed today with the corresponding supported reagents [2]. The commercial availability of almost every kind of functionality in a supported form (from oxidizing to reducing agents, to acids and bases, catalysts, chiral auxiliaries, and so on) makes the use of PASPS particularly versatile and attractive to organic chemists.

Microwave-assisted organic synthesis

Since the late 1990s, MAOS has become a forefront support for rapid optimization of reactions, for the efficient synthesis of new chemical entities and for discovering and probing new chemical reactivity.

MAOS is mainly based on the efficient heating of materials by the microwave dielectric heating effect (through dipolar polarization and ionic conduction) [3].

The use of microwave irradiation offers significant advantages:

- higher reaction temperatures by combination of microwave heating with sealed vessels;
- reduced reaction times, higher yields and cleaner reaction profiles;
- the use of lower boiling point solvents under pressure in sealed vessels;
- specific heating of strongly microwave-absorbing metal catalysts;
- more reproducible experimental conditions by accurate control of temperature and pressure profile.

Starting from early reports of microwave-promoted Suzuki coupling [4], a wide variety of reactions have benefited from MAOS and organic reactivity with microwaves has been extensively explored [5].

MAOS may be advantageously coupled to inorganic-supported solvent-free conditions, thus simplifying work-up procedures (in many cases the pure expected products can be obtained directly by simple extraction, distillation or sublimation) and waste disposal [6,7].

Similarly, the combination of MAOS and solid-supported organic synthesis or PASPS [8] can be performed. Usually, the synthetic steps involving polymeric supports require repeated runs and longer reaction times than the corresponding solution-phase protocols, to reach high conversions. Microwave heating again allows reduction of reaction times and improvement of the loading of the functionalized solid support, employing not only traditional polystyrene supports but also soluble polymers and fluorous phase synthesis.

The main issue associated with MAOS is the scalability of the process. Large-batch reactors [9], as well as continuous-flow mode [10] have been described. However, the scalability of microwave reactions still requires more development, especially in the technology and engineering field.

Flow chemistry

In flow chemistry, a chemical reaction is performed in a continuously flowing stream in a network of interconnecting tubes: where tubes join one another, the fluids come into contact and the reaction takes place [11]. In flow processes, dosing time is eliminated, thus resulting in constant mixture composition and avoiding accumulation of unreacted reagents. Heat transfer is almost immediate in a flow system, so temperature control is more accurate with major benefits especially for runaway reactions. Overall, side reactions are considerably reduced and safety is improved. Linear, divergent as well as convergent multistep syntheses are also feasible by assembling a line of flow reactors, provided that solvent switching is not required and that the flow rate can ensure full conversion of the starting material in each step.

The main issue associated with flow technologies is that reagents and products must be soluble in the solvent flow, since flow systems are incompatible with precipitating products (especially when microfluidic systems are involved): it is often necessary, therefore, to work with very dilute solutions.

Microreactors (i.e. flow reactors with micrometer scale) have become commonly employed in organic synthesis, both in research chemistry and in process development [12]. The small dimensions of microreactors allow the use of minimal amounts of reagents under precisely controlled conditions, and rapid screening of reaction conditions with improved safety. In order to obtain synthetically useful amounts of material, the microreactors are simply allowed to run for a longer period of time ('scale-out'), or several reactors are placed in parallel ('numbering up').

Owing to the possibility of producing a large number of compounds in high purity and in short time, microreactors have been employed successfully in combinatorial chemistry [13], allowing the rapid synthesis of combinatorial arrays [14,15] and also their on-line purification by chromatography [16]. The concept can be extended to also include high-throughput assays in the flow system, in order to speed up the entire hit identification and lead optimization process [17].

Examples of laboratory flow systems operating in a larger scale than microreactors have been recently described and are becoming commonly used in organic synthesis.

In particular, the use of flow catalytic heterogeneous hydrogenation has found wide application, since this technology has recently become commercially available. The supported catalyst is usually confined in a disposable cartridge and the hydrogen gas is generated *in situ*, so that flow hydrogenation becomes safer than traditional batch protocols. Literature reports confirmed significant advantages when compared to batch hydrogenation reactions, in terms of reaction rate, efficiency and by-products profile [18–20].

Many examples in the field of organic synthesis and multigram scale preparations have been also reported [21,22], entailing the use of sensitive reagents (such as chiral transfer hydrogenation catalysts [23] or organozinc reagents [24]). Flow-through processes can be advantageously coupled with polymer-supported reagents and scavengers [25] and also with supported enzymes [26].

Continuous-flow processes also display significant advantages during scale-up and development in process chemistry: the problems strictly related to scale-up of batch operations [27] (such as accurate control of the reaction time and mixing during crucial

additions, safety of runaway reactions) can be more easily faced thanks to the careful control of reaction parameters allowed by flow processes [28].

Combined technologies

The best results can often be obtained with the combination of the advantages of two or more of these techniques, thus further improving and enhancing the efficacy of each approach. For example, synthesis of an array of biphenyl derivatives by Suzuki coupling with supported catalyst under microwave irradiation in flow mode has been recently described [29]. The supported catalyst showed enhanced reactivity when used with microwave heating, while poorer results were obtained with conventional heating. Moreover, the use of a flow reactor ensures higher purities than with the traditional batch mode, thanks to very short reaction times in which the local effective catalyst concentration is very high. The proposed protocol and system proved to be very versatile: reactions can be performed in automated sequences for the synthesis of compound arrays or, alternatively, large-scale production can be achieved by running the system for many hours (Fig. 1).

Breakthrough reactions

In the past decade, the discovery of new reactions and the improvement of synthetic approaches have opened the way for the preparation of new and complex chemical structures. We would like to highlight here three breakthrough approaches that have entered in the portfolio of common chemical reactions used by medicinal chemists: click chemistry, multicomponent reactions (MCRs) and ring-closing metathesis (RCM).

The improvements that these strategies have introduced include high chemical efficiency and selectivity, good versatility and operational simplicity.

Click chemistry

In 2001, Sharpless *et al*. introduced the concept of 'click chemistry' as a set of powerful, highly reliable and selective reactions for the rapid synthesis of new compounds and combinatorial libraries [30], as summarized by the same authors as follows: 'through the use of only the most facile and selective chemical transformations, click chemistry simplifies compound synthesis, providing the means for faster lead discovery and optimization. A click reaction must be of wide scope, giving consistently high yields with a variety of starting materials. It must be easy to perform, be insensitive to oxygen or water, and use only readily available reagents. Reaction work-up and product isolation must be simple, without requiring chromatographic purification' [31]. Moreover, click reactions must generate only inoffensive by-products, use no solvent or only benign or easily removable solvents and the products must be stable under physiological conditions.

The click-chemistry approach is then more a philosophy than a definite group of reactions. However, it is possible to list some reactions having the cited requirements:

- cycloadditions of unsaturated species, especially 1,3-dipolar cycloaddition reactions, and Diels–Alder transformations;

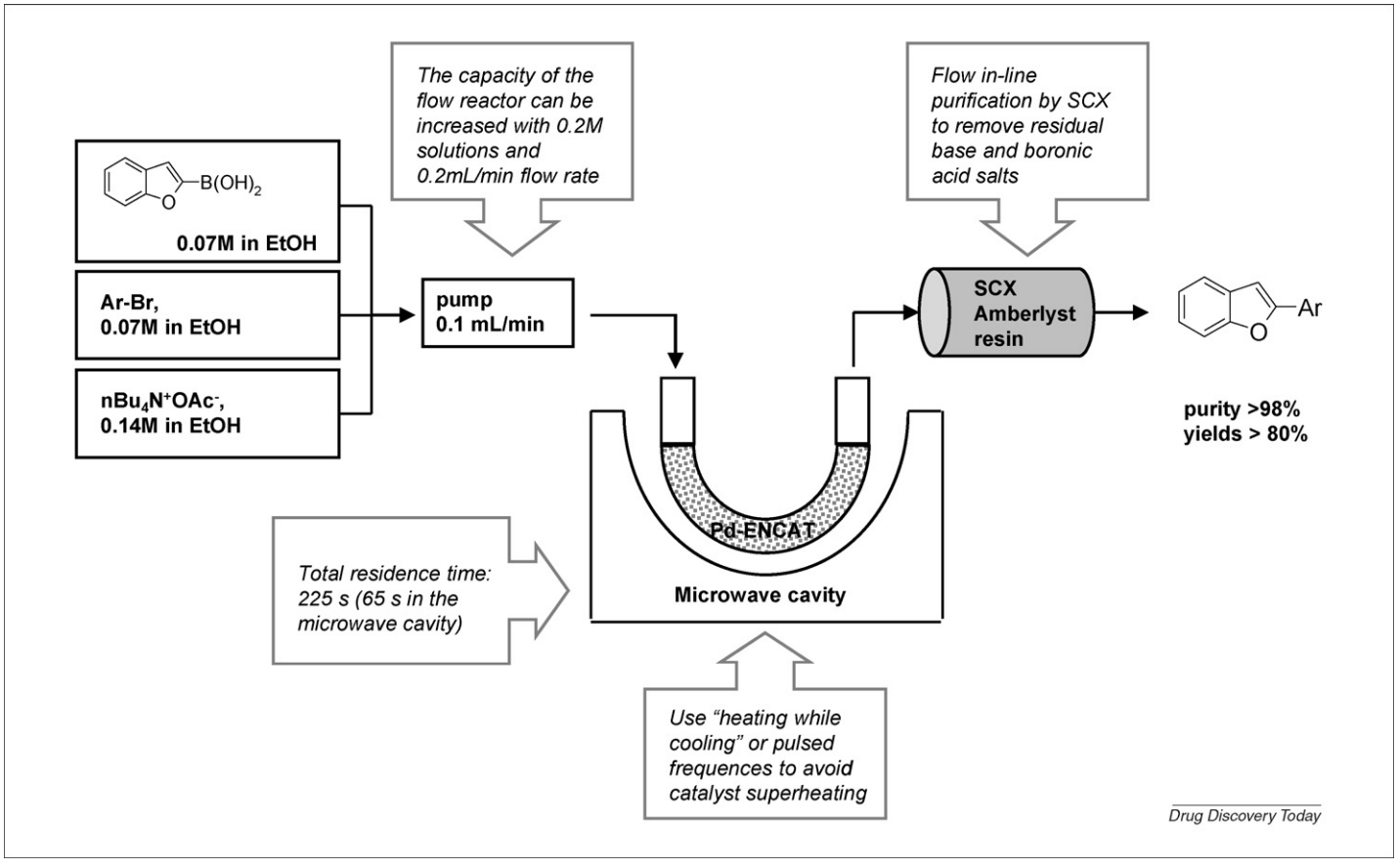


FIGURE 1

Example of combined technology: PASPS, MAOS and flow chemistry.

- nucleophilic substitution chemistry, particularly ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions and episulfonium ions;
- carbonyl chemistry of the 'nonaldol' type, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones and amides;
- addition to carbon–carbon multiple bonds, especially oxidative reactions such as epoxidation, dihydroxylation, aziridination and sulfenyl halide addition, but also Michael addition of nucleophilic reactants.

A common and fundamental feature of this selection of reactions is the preparation of a product obtained by the clear and complete addition of the reactants without the generation of by-products that require an accurate purification step. This concept blends in perfectly with Trost's atom economy theory, which describes the efficacy of a chemical process in term of balance of all atom involved [32]: in an ideal process, the amount of starting materials equals the amount of all generated products and no atom is wasted.

All the aforementioned classes of reactions are useful tools for the synthesis of biologically relevant molecules, but in this paper we will focus our attention on 1,3-dipolar cycloadditions, especially notable for their ability to produce small cycles containing heteroatoms. One of the most useful and studied 1,3-dipolar click reactions in drug discovery is undoubtedly the Huisgen dipolar cycloaddition of azides and alkynes [33,34]. The importance of this cycloaddition is due to the heterocyclic products obtained. 1,2,3-Triazoles are very interesting moieties in medicinal chemistry, since they may act as rigid linking units, mimicking the atom placement and the electronic properties of a peptide bond, but without the same liability to hydrolytic cleavage.

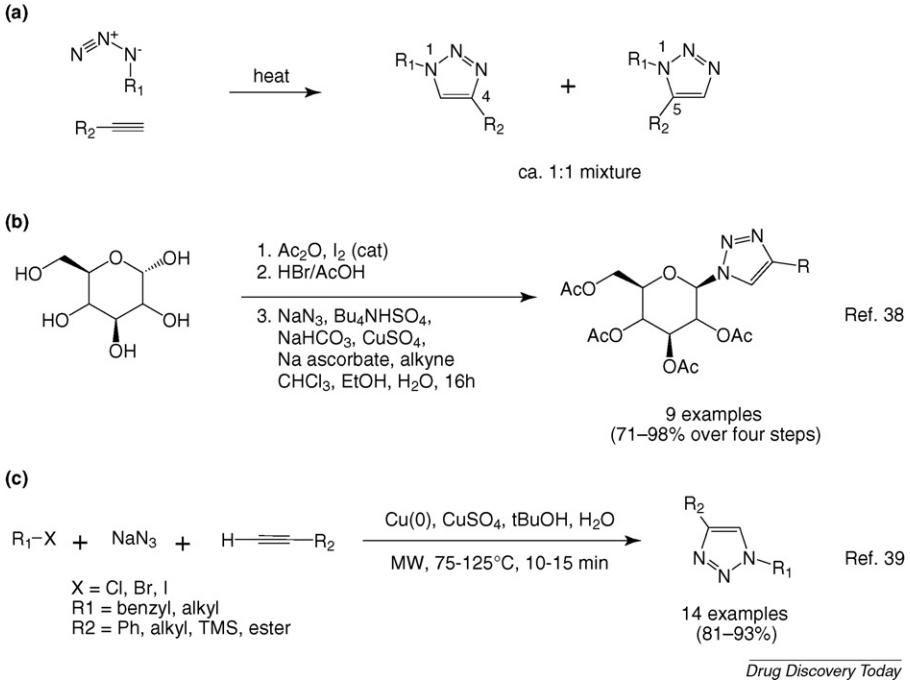
Azides and alkynes are essentially inert to most organic conditions and their kinetic stability is responsible for their low reactivity. The reaction between these two species generally requires elevated temperatures and long reaction times; moreover, the cycloaddition affords a mixture of the two possible 1,4- and 1,5-regioisomers (Scheme 1a).

In 2002 Sharpless' [35] and Meldal's [36] groups reported independently the advantages of Cu(I)-catalyzed alkyne–azide cycloaddition. Copper(I) catalysis improves the regioselectivity, affording exclusively the 1,4-isomer, and increases the reaction rate, thus avoiding also the necessity of high temperatures.

With this new protocol, the Huisgen dipolar cycloaddition can be considered a true click-chemistry reaction, entailing high reaction rates, complete atom economy and pure products. It then becomes a useful instrument for the preparation of biologically active compounds.

Since copper(I) salts are quite labile, the active catalytic species is usually generated *in situ*. The most used protocols involve the reduction of more stable and cheaper copper(II) salts with sodium ascorbate and the comproportionation of Cu(II)/Cu(0) species. Some explicative examples of the use and of the potentiality of the copper-catalyzed Huisgen cycloaddition are depicted in Scheme 1b,c. Moreover, following a peculiar medicinal chemistry strategy, a successful example of mimicking replacement of the amide bond with a triazole moiety was reported by Kim *et al.* on analogs of ceramide [37].

In order to access 1,5-substituted triazoles, the same authors that introduced the click-chemistry concept proposed two alternative synthetic approaches: the first one is based on the reaction of bromomagnesium acetylides with organic azides [38–40], which cannot be considered a click-chemistry reaction, because it entails scarce atom economy and it leads to the formation of by-products that require a purification step. In a second approach, azides and alkynes are reacted in the same conditions described for the classical Huisgen protocol, but with a different catalyst. Ruthenium



SCHEME 1

Huisgen azide–alkynes cycloadditions: **(a)** general thermal reaction and **(b, c)** examples of Cu(I)-catalyzed couplings.

complexes, and particularly pentamethyl-cyclopentadienyl ruthenium chloro-bis(triphenylphosphine) ($Cp^*RuCl(PPh_3)_2$), afford the expected 1,5-products in high yields and as the only isomers [41].

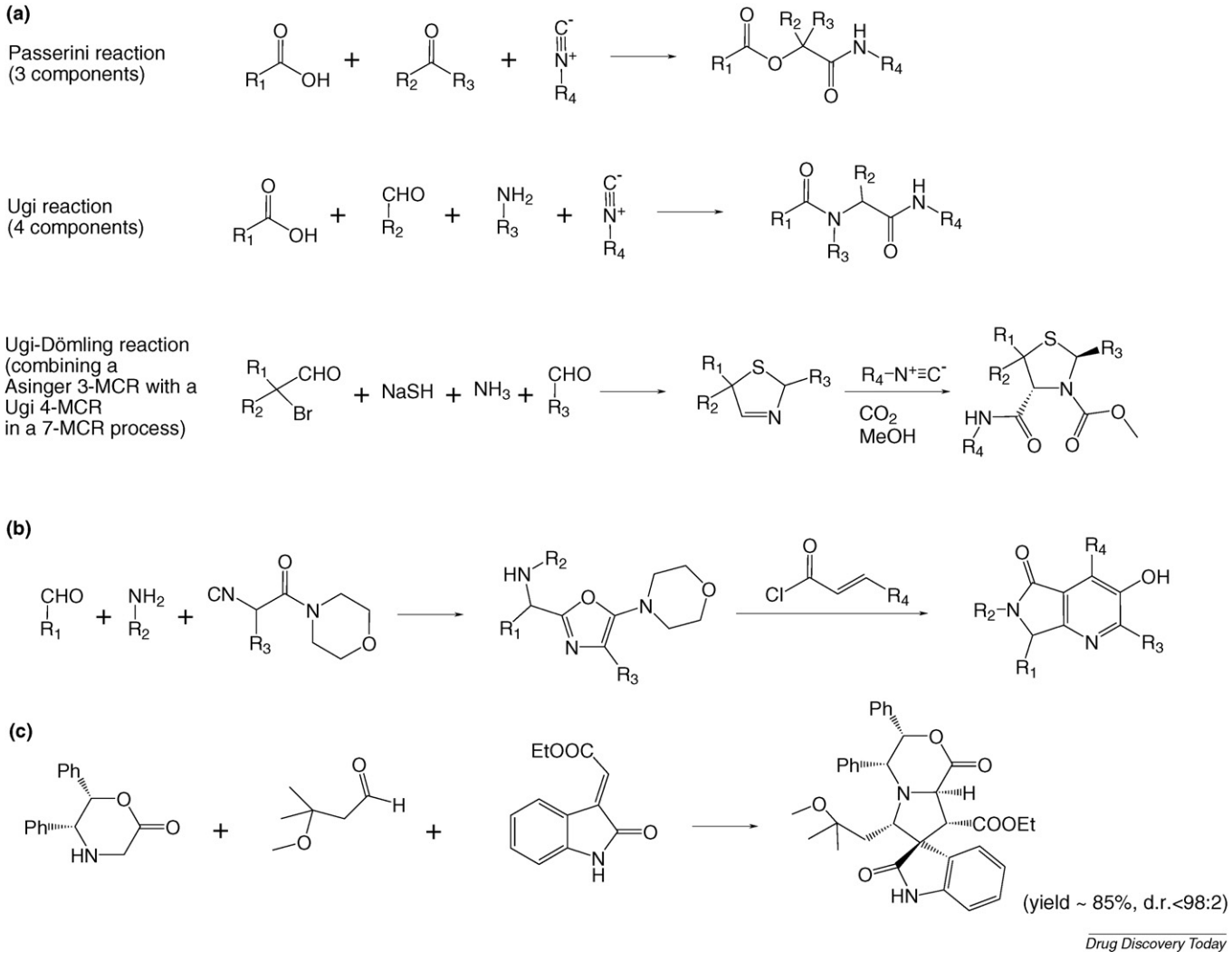
Thanks to this new protocol, it is now possible to modulate the regioselectivity of the process by simple metal catalyst selection. In this way, the catalyzed Huisgen cycloaddition, a classical example of click chemistry, is a complete, versatile and accessible method for the preparation of compounds featuring the 1,2,3-triazole ring, with various substitution patterns.

Multicomponent reactions

MCRs are convergent reactions, involving three or more starting materials that yield a single product (bringing features from all the reagents) in a single event, with a one-pot procedure. From a medicinal chemistry perspective, this typology of reaction is particularly advantageous, because it allows the easy, fast and high-throughput synthesis of diverse compounds, as well as a rapid exploration of the chemical space with a limited synthetic effort. MCRs can find wide application in the whole drug discovery process, starting from the hit generation phase (where they allow the rapid synthesis of large and diverse compound collections) to the lead optimization phase (with the rapid and efficient exploration of the chemical space around a given scaffold). The scale-up operations and optimization during the development phase are also significantly shortened and simplified with MCRs.

The early discovery of MCRs was based on the chemistry of isocyanides, with the three-component Passerini reaction, described in 1921 [42], and the four-component Ugi reaction, discovered in 1959 [43]. The use of isocyanides in MCRs has been extensively exploited during the past 80 years [44,45], up to the discovery of a seven-component reaction by Dömling and Ugi [46] (Scheme 2a). As reported in the cited general reactions, it is quite simple to generate a lot of different final products by a single cascade process. For example, in a typical four-component Ugi reaction, using only five reactants for each functional group, the number of final diamide compounds is $5 \times 5 \times 5 \times 5 = 625$.

A large number of products obtained by MCRs have found successful application in drug discovery [47]. During recent years, an increasing number of new MCRs have been discovered, involving many reactive species other than isocyanides. Many examples



SCHEME 2

(a) From the first isocyanide-based MCRs to Ugi–Dömling 7-MCR; **(b)** three- and four-component syntheses of 5-aminooxazole and pyrrolopyridin-5-one derivatives **(c)** diastereoselective MCR based on 1,3-dipolar cycloaddition reaction.

have been reported, especially in the synthesis of substituted heterocyclic structures, which are particularly interesting for medicinal chemistry (see for example the synthesis of 5-aminooxazole and pyrrolopyridin-5-one derivatives reported in Scheme 2b) [48]. Moreover, further elaboration of MCR products resulted in the synthesis of complex structures, also including natural products [49]. Extensive studies on asymmetric multicomponent reactions (AMCRs) have been reported, resulting in diastereo- and enantioselective syntheses with one-pot procedures [50].

With the aim of illustrating the utility and the potential of this chemistry approach, an example of the preparation of natural products via a diastereoselective three-component reaction, not involving the above-mentioned isocyanides, is shown in Scheme 2c [51].

In a continuous effort to improve the existing synthetic methodologies, the search for new MCRs plays an important role in the synthesis of new and complex structures. Interestingly, although most of the older known MCRs have been found by serendipity, a theoretical approach to the discovery of new MCRs has also been described, thus confirming the great interest of pharmaceutical companies in this approach [52].

Ring-closing metathesis

The huge importance of olefin metathesis, both in industrial and in research areas, was recognized by the Nobel Committee, which, in 2005, awarded Prof Chauvin (France), Prof Grubbs (USA) and Prof Schrock (USA) 'for the development of the metathesis method in organic synthesis'.

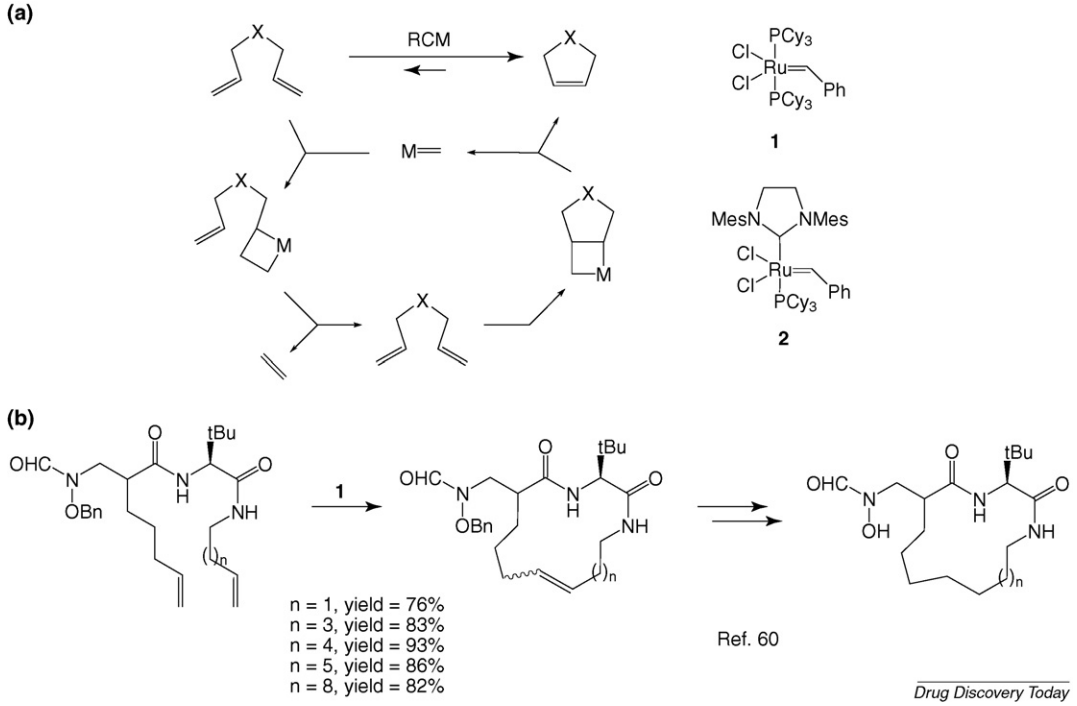
Metathesis reactions have a variety of applications including both ring closure and ring opening, both the synthesis of single compounds and polymerization. In this review, only RCM will be treated, and in particular, some applications regarding biologically active molecules [53], leaving to the reader the study of the involved reaction mechanism and of further synthetic applications and strategies [54–57].

The RCM reaction entails the cyclization of two terminal olefins in a chain, affording a C=C double bond, whose stereoselectivity depends on the ring size and the effect of chain substituents. The cyclization step gives, as by-product, a molecule of alkene, usually ethylene, which leaves the reaction mixture, driving the equilibrium process to complete conversion. Both small rings (5-, 6- and 7-membered) and macrocycles (with more than 10–12 members) can be formed, involving heteroatoms and different functional groups.

The RCM catalysts are metallo-carbenes (usually molybdenum, ruthenium and tungsten) that form metallo-cyclobutane intermediates. These intermediates evolve to the expected cyclic product, restoring the active catalyst (Scheme 3a).

Nowadays, the most frequently used catalysts are ruthenium–carbene species, such as Grubbs first- and second-generation catalysts (**1** and **2**, Scheme 3) [58–60]. The easy accessibility and the moderate price of these precatalysts have allowed a wide growth of metathesis applications both in academic and industrial areas.

RCM has found large applicability in medicinal chemistry thanks to the mild reaction conditions, the tolerance toward many functional groups and the possibility of preparing different sized rings. This last point is essential in medicinal chemistry, because the cyclization reduces the number of rotatable bonds, increasing, in many cases, the metabolic stability, the efficacy and the selectivity of the biologically active molecule. In this way, metathesis reactions are used by medicinal chemists in order to prepare both small sized rings, also containing heteroatoms, and larger rings, typical of natural products arising, for example, from marine sponges, corals and so on.



SCHEME 3

(a) General pathway of RCM and the two most used precatalysts; **(b)** synthesis of a set of macrocyclic pseudo-peptides as potential inhibitors of deformylase via RCM.

An example of macrocyclic ring formation, reported in Scheme 3b, would better exemplify the potential of this synthetic strategy.

The main drawback of the RCM protocol is the low stability of the active ruthenium–carbene species in the reaction mixture, especially at elevated temperatures. This loss of activity often requires subsequent additions of fresh precatalyst, in order to complete the ring-forming process. As a consequence, the reaction mixture may contain a consistent amount (up to 30%) of catalyst by-products, which requires accurate purification. For example, metallic impurities, such as toxic ruthenium oxides, must be completely eliminated, because of their side effects on biological assays, particularly *in vivo*. Anyway, the required accurate purification step is negligible compared to the huge synthetic benefits produced by this protocol.

Perspectives and conclusions

In order to improve the efficiency of medicinal chemistry, new technologies applied to organic synthesis are deeply changing the traditional operating procedures in chemistry laboratories. Flow chemistry, in particular, represents a substantial revolution in everyday laboratory practice, for its general applicability and its possible combination with other technologies such as PASPS and microwave heating. Simultaneously, new synthetic strategies and revisited classical reactions have been employed to achieve new and variously decorated compounds faster: in this perspective, the click-chemistry concept and MCRs represent two different, but conceptually similar, solutions to the same problem.

Besides the evolution of synthetic techniques and strategies discussed above, the necessity of accurate and fast analytical determination of chemicals has also improved the technologies and the methodologies associated with analytical instrumentations. High-performance liquid chromatography combined with mass spectrometry (HPLC–MS) is the analytical technique that has received the greatest impulse from this point of view and, currently, it may be considered the technique of choice for most assays used in various stages in drug discovery [61]. With the aim of decreasing analysis times maintaining high resolutions, new high-performance stationary phases have been developed. Moreover, improved technologies, such as ultra performance liquid chromatography (UPLC) [62] and supercritical fluid chromatography (SFC, widely used also in the purification steps) [63], contributed to enhance analytical efficiency.

In conclusion, we would like to remind here that, as quoted by Sharpless *et al.* [30]: 'The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties.' (George S. Hammond, Norris Award Lecture, 1968). If useful properties are our goal – for example, better pharmaceuticals – then the use of complicated synthetic strategies is justified only if they provide the best way to achieve those properties. Thus, the discovery of new synthesis or technologies for medicinal chemistry must constantly focus on the need for simplification and constant process improvement to provide novel and better molecules.

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