1
General Introduction to MCRs: Past, Present, and Future

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1.1
Introduction

Multicomponent reactions (MCRs) are generally defined as reactions in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product [1]. Their usefulness can be rationalized by multiple advantages of MCRs over traditional multistep sequential assembly of target compounds. In MCRs, a molecule is assembled in one convergent chemical step in one pot by simply mixing the corresponding starting materials as opposed to traditional ways of synthesizing a target molecule over multiple sequential steps. At the same time, considerably complex molecules can be assembled by MCRs. This has considerable advantages as it saves precious time and drastically reduces effort.

MCRs are mostly experimentally simple to perform, often without the need of dry conditions and inert atmosphere. Molecules are assembled in a convergent way and not in a linear approach using MCRs. Therefore, structure–activity relationships (SARs) can be rapidly generated using MCRs, since all property-determining moieties are introduced in one step instead of sequentially [2]. Last but not least, MCRs provide a huge chemical diversity and currently more than 300 different scaffolds have been described in the chemical literature. For example, more than 40 different ways to access differentially substituted piperazine scaffolds using MCRs have been recently reviewed [3].

Although MCR chemistry is almost as old as organic chemistry and was first described as early as 1851, it should be noted that early chemists did not recognize the enormous engineering potential of MCRs. However, it took another >100 years until Ivar Ugi in a strike of a genius discovered his four-component condensation and also recognized the enormous potential of MCRs in applied chemistry (Figure 1.1) [4].

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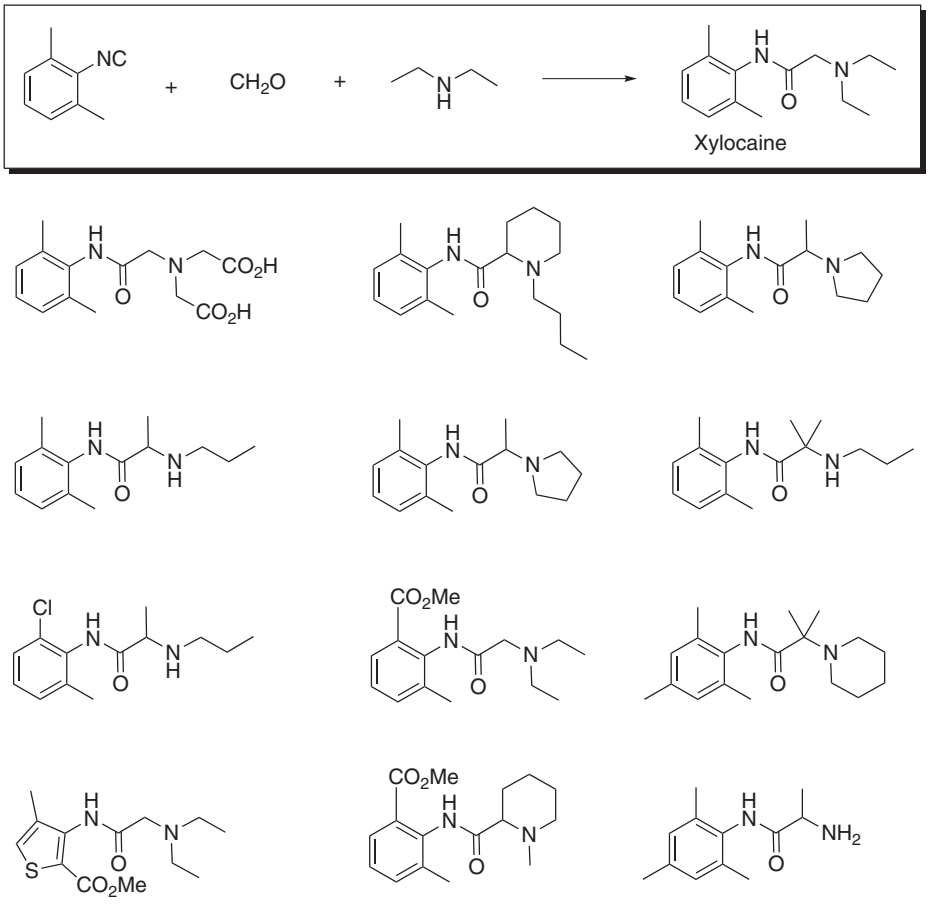

Figure 1.1 A three-component reaction toward the local anesthetic xylocaine and the first combinatorial library of small molecules proposed by Ivar Ugi in the 1960.

1.2 Advances in Chemistry

Many MCRs have been described in the past one and a half century and recently not many fundamental advances in finding new MCRs have been made [5–7]. A strategy to enhance the size and diversity of current MCR chemical space is the concept of combining a MCR and a subsequent secondary reaction, also known as postcondensation or Ugi–deprotection–cyclization (UDC) [2]. Herein, bifunctional orthogonally protected starting materials are used and ring cyclizations can take place in a secondary step upon deprotection of the secondary functional groups. Many different scaffolds have been recently described using this strategy. One example is shown in Figure 1.2.

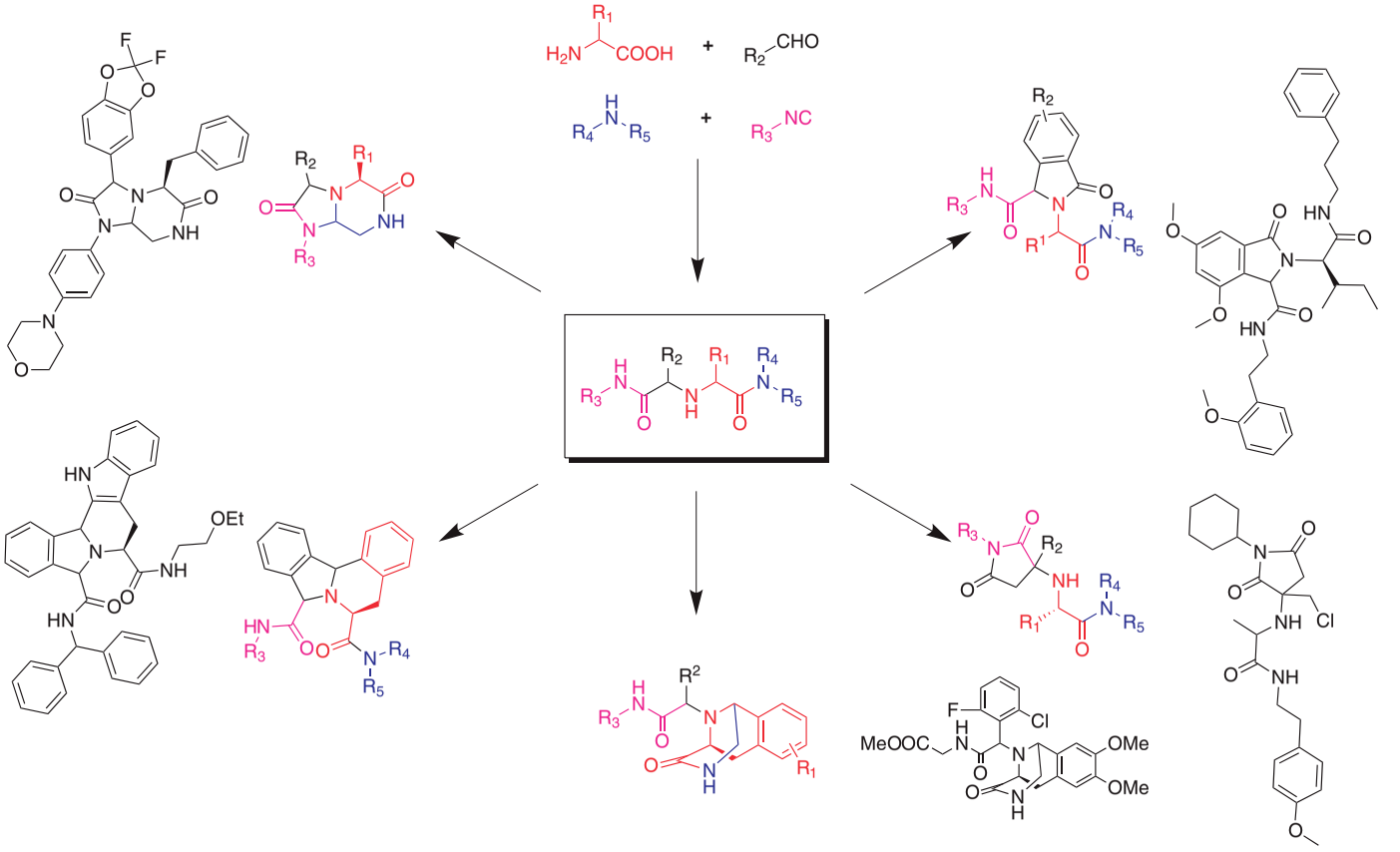

Figure 1.2 Discovery of the Ugi-5C-4CR variation employing unprotected α-amino acids, oxo components, primary or secondary amines, and isocyanides, and the synthesis of several heterocyclic scaffolds using orthogonally protected bifunctional starting materials. Generalized scaffolds are shown in color, and synthesized examples in black and white.

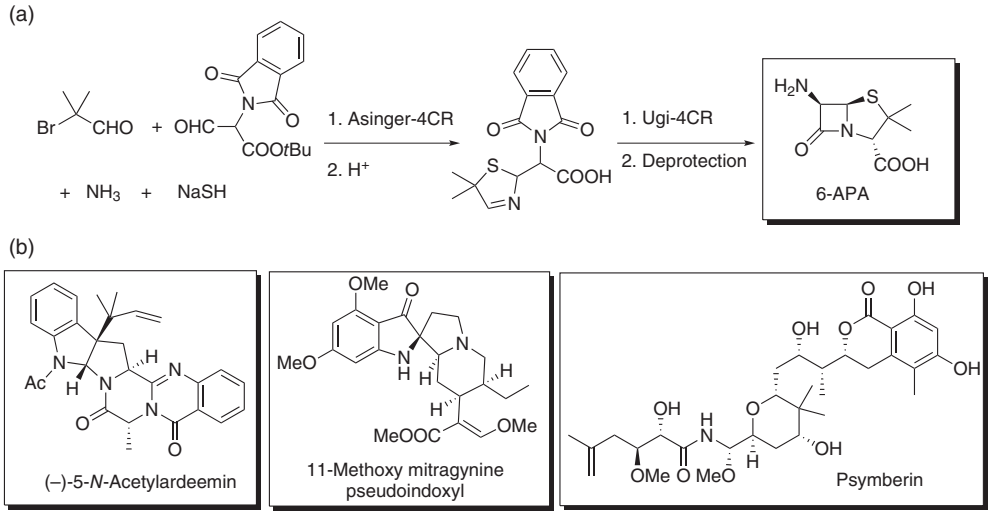

Figure 1.3 (a) The union of the Asinger-4CR and the Ugi-4CR allows for the convergent and fast assembly of 6-aminopenicillanic acid natural product. (b) Recent synthetic targets of MCR natural product chemistry.

It is based on a recently discovered variation of the Ugi reaction of α-amino acids, oxo components, and isocyanides, now including primary and secondary amines [8–10].

1.3 Total Syntheses

While the Bucherer–Bergs and the related Strecker synthesis are well-established methods for the one-pot synthesis of natural and unnatural amino acids, the complex antibiotic penicillin was synthesized 50 years ago in a highly convergent approach by Ivar Ugi by using two MCRs, the Asinger reaction and his own reaction (Figure 1.3) [11]. Other recent natural product targets using MCR as a key step in their synthesis are also shown in Figure 1.3. Although early example of the advantageous use of MCR in the conscious total synthesis of complex natural products leads the way, its use has been neglected for decades and only recently realized by a few organic chemists [12–17].

1.4 Applications in Pharmaceutical and Agrochemical Industry

Two decades ago, MCR chemistry was almost generally neglected in pharmaceutical and agro industry. The knowledge of these reactions was often low and it

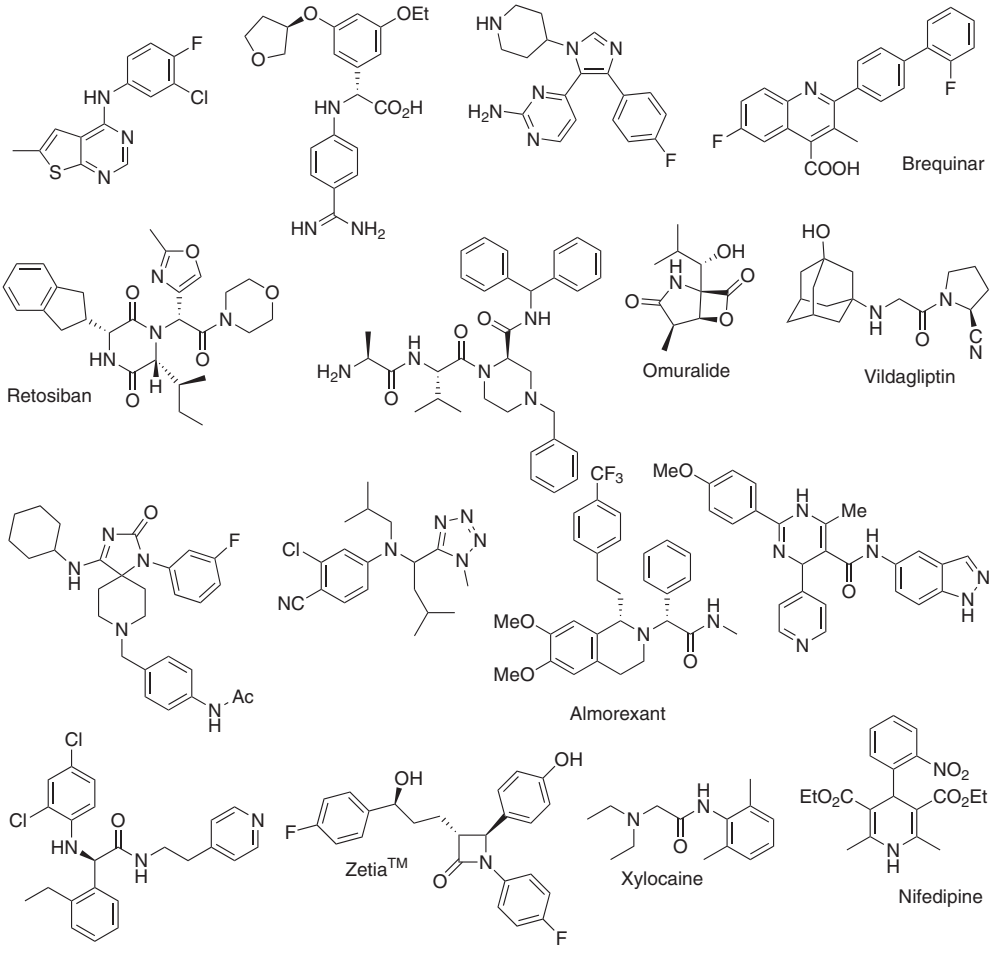

Figure 1.4 Examples of marketed drugs or drugs under (pre)clinical development and incorporating MCR chemistry.

was generally believed that MCR scaffolds are associated with useless drug-like properties (absorption, distribution, metabolism, excretion, and toxicity (ADMET)). Now MCR technology is widely recognized for its impact on drug discovery projects and is strongly endorsed by industry as well as academia [18]. An increasing number of clinical and marketed drugs were discovered and assembled by MCR since then (Figure 1.4). Examples include nifedipine (Hantzsch-3CR), praziquantel, or Zetia™. Two oxytocin receptor antagonists for the treatment of preterm birth and premature ejaculation, epelsiban and atosiban, are currently undergoing human clinical trials. They are both assembled by the classical Ugi MCR [19–21]. Interestingly, they show superior activity for the oxytocin receptor and selectivity toward the related vasopressin receptors

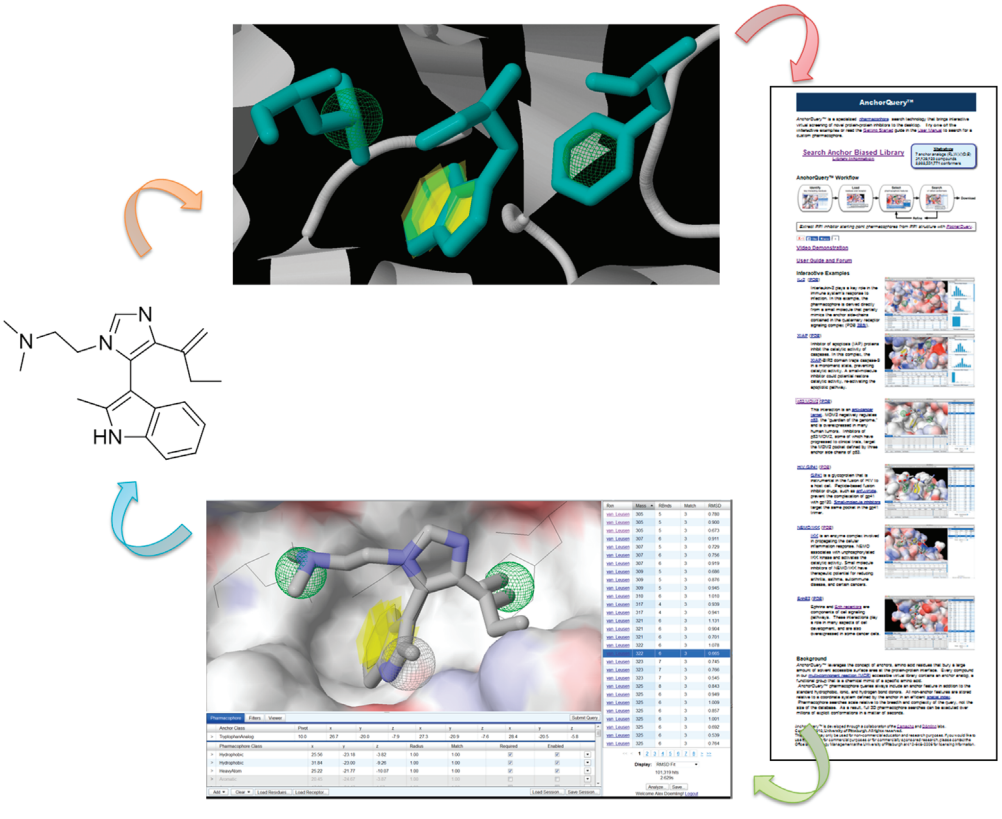

Figure 1.5 MCR-based computational methods can help to effectively query the very large chemical MCR space. Clockwise: generation of a pharmacophore model based on a 3D structure, screening of the pharmacophore model against a very large MCR 3D compound database (AnchorQuery), synthesis, and refinement of hits.

than the peptide-based compounds currently used clinically. Perhaps against the intuition of many medicinal chemists, the Ugi diketopiperazines are orally bioavailable, while the currently used peptide derivatives are i.v. only and must be stabilized by the introduction of terminal protecting groups and unnatural amino acids. An example of a MCR-based plant protecting antifungal includes mandipropamide [22]. These examples show that pharmaceutical and agrochemical compounds with preferred ADMET properties and superior activities can be engineered based on MCR chemistry.

The very high compound numbers per scaffold based on MCR may be regarded as friend or foe. On the one hand, it can be fortunate to have a MCR product as a medicinal chemistry starting point, since a fast and efficient SAR elaboration can be accomplished; on the other hand, the known chemical space based on MCRs is incredibly large and can neither be screened nor exhaustively synthesized with reasonable efforts. The currently preferred path

to medicinal chemistry starting points in industry, the high-throughput screening (HTS), however, is an expensive process with rather low efficiency yielding hits often only in low double-digit or single-digit percentage. Modern postgenomic targets often yield zero hits. The initial hits are often ineffective to elaborate due to their complex multistep synthesis. Thus, neither the screening even of a very small fraction of the chemical space accessible by the classical Ugi-4CR and other scaffolds, nor the synthesis is possible. Recent advances in computational chemical space enumeration and screening, however, allow for an alternative process to efficiently foster a very large chemical space. The free web-, anchor-, and pharmacophore-based server AnchorQuery™ (anchorquery.ccbb.pitt.edu/), for example, allows for the screening of a very large virtual MCR library with over a billion members (Figure 1.5) [23]. AnchorQuery builds on the role deeply buried amino acid side chains or other anchors play in protein–protein interactions. Proposed virtual screening hits can be instantaneously synthesized and tested using convergent MCR chemistry. The software was instrumental to the discovery of multiple potent and selective MCR-based antagonists of the protein–protein interaction between p53 and MDM2 [24–26]. Thus, computational approaches to screen MCR libraries will likely play a more and more important role in the early drug discovery process in the future.

More and more high-resolution structural information on MCR molecules bound to biological receptors is available (Figure 1.6) [18]. With the advent of

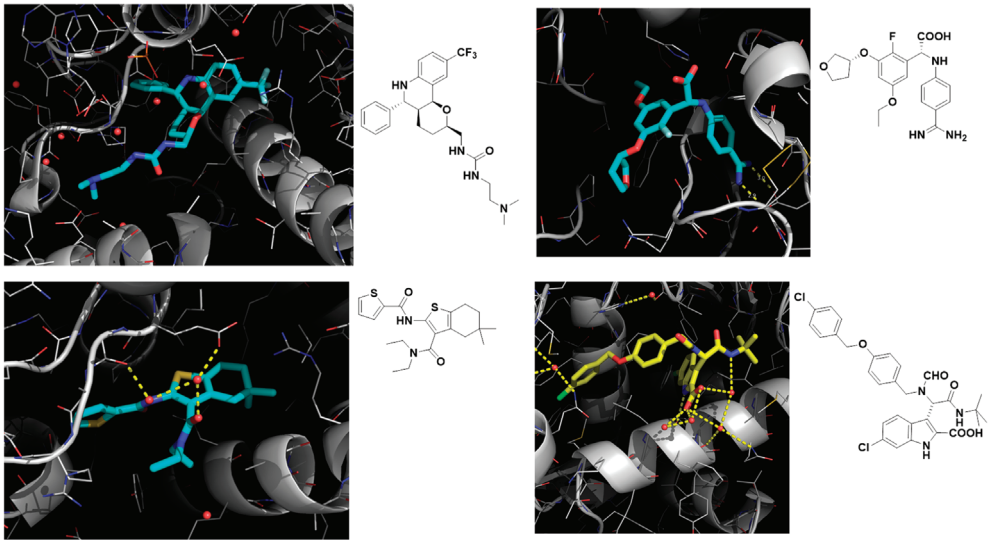

Figure 1.6 Examples of cocrystal structures of MCR molecules bound to biological receptors. Clockwise left: Povarov-3CR molecule bound to kinesin-5 (PDB ID 3L9H) [27], Ugi-3CR molecule bound to FVIIa (PDB ID 2BZ6) [28], Ugi-4CR molecule bound to MDM2 (PDB ID 4MDN) [26], and Gewald-3CR molecule targeting motor protein KSP (PDB ID 2UYM) [29].

structure-based design and fragment-based approaches in drug discovery, access to binding information of MCR molecules to their receptors is becoming crucial. Once the binding mode of a MCR molecule is defined, hit-to-lead transitions become more facile and time to market can be shortened and attrition rate in later clinical trials can be potentially reduced.

Other worthwhile applications of MCRs in medicinal chemistry are in route scouting for shorter, convergent, and cheaper syntheses. An excellent showcase is the synthesis of the recently approved HCV protease inhibitor telaprevir [30]. The complex compound is industrially produced using a lengthy, highly linear strategy relying on standard peptide chemistry exceeding 20 synthetic steps. Orru and coworkers were able to reduce the complexity of the synthesis of telaprevir by almost half using a biotransformation and two multicomponent reactions as the key steps. Another example is the convergent synthesis of the schistosomiasis drug praziquantel using key Ugi and Pictet–Spengler reactions (Figure 1.7) [31]. Clearly, more synthetic targets are out there, which can be

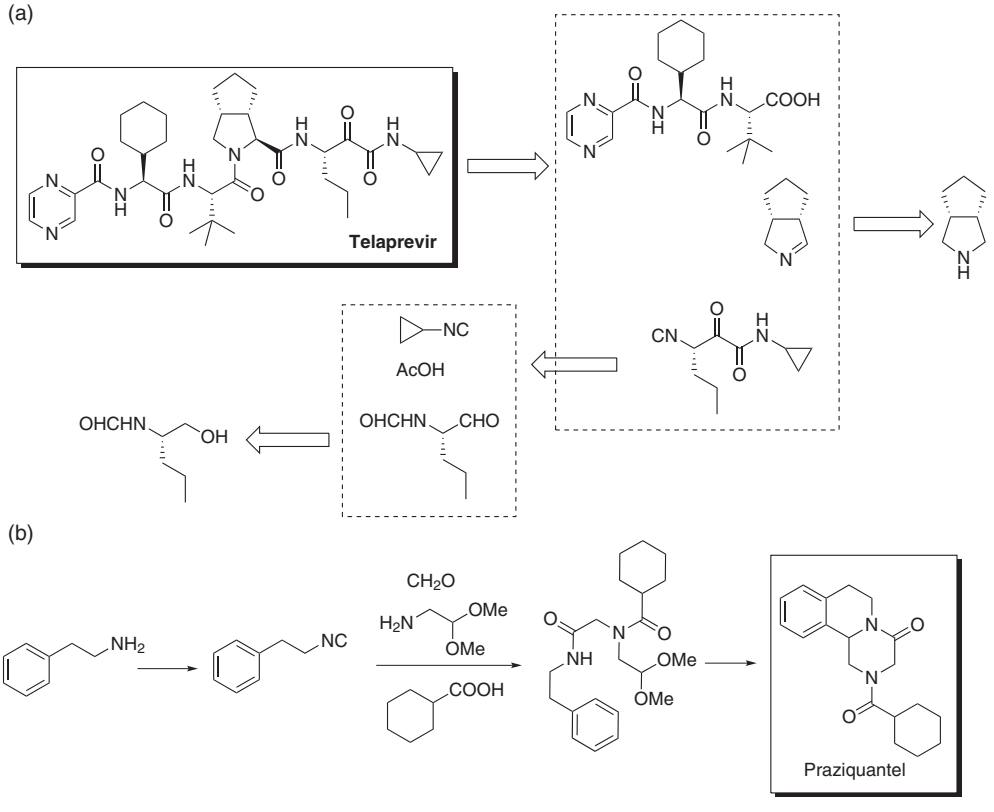

Figure 1.7 Use of MCR chemistry for the easy and cheap synthesis and process improvement of marketed drugs. (a) Telaprevir structure and MCR retrosynthesis. (b) Three-step praziquantel synthesis involving Ugi and Pictet–Spengler reactions.

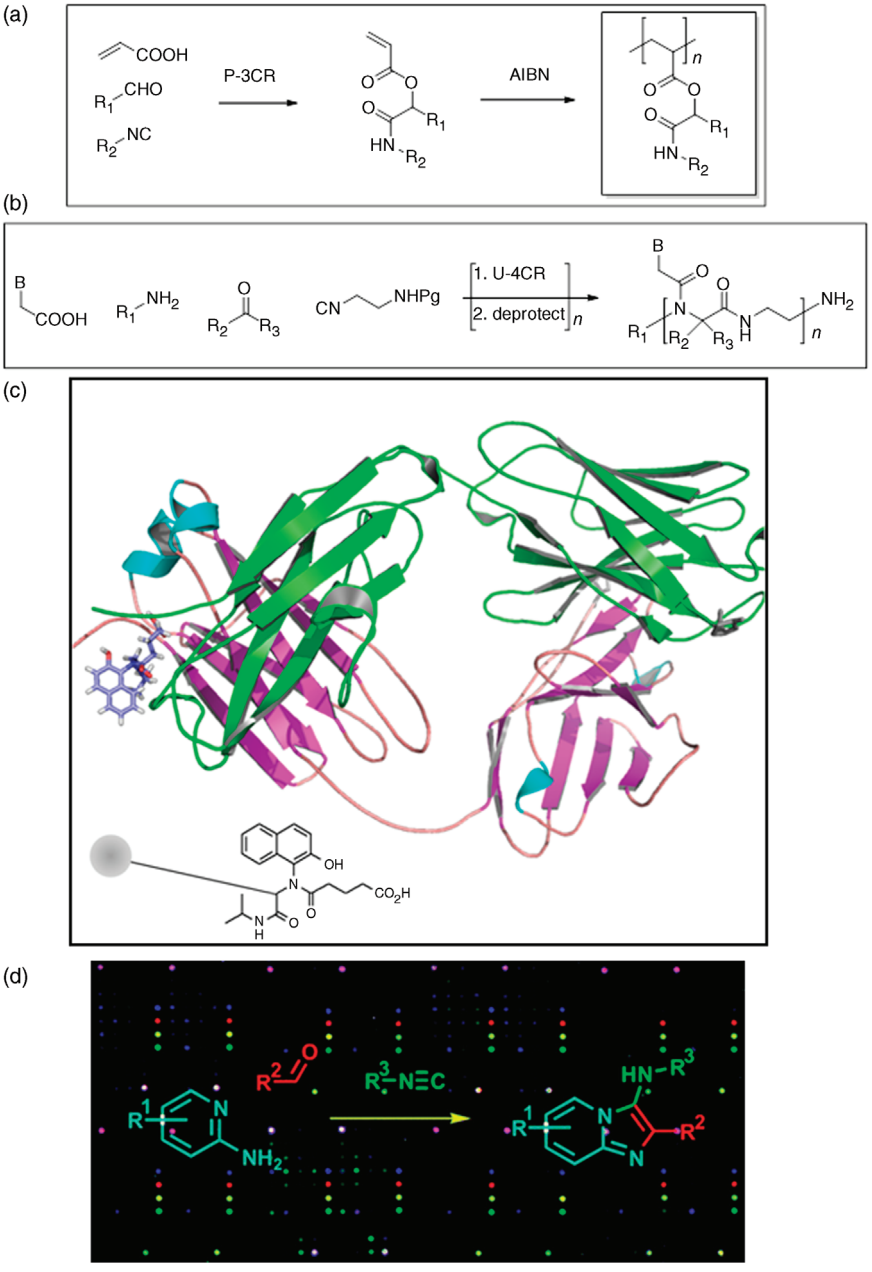

Figure 1.8 Examples of the use of MCRs in material chemistry. (a) Sequence-specific polymer synthesis as exemplified for Passerini reaction-derived acrylic acid monomers. (b) PNA synthesis using the sequential Ugi reaction. (c) Sepharose solid support-bound Ugi products for the affinity purification of therapeutic Fab fragments. Docking of the best Ugi ligand (blue sticks) into human Fab fragment. (d) GBB-3CR-derived fluorescent pharmacophores.

potentially accessed in a more convergent and cheaper way using MCR chemistry, thus potentially benefitting the patient.

1.5 Materials

Another application of MCR chemistry far from being leveraged to its full extent is in materials science (Figure 1.8). Precise engineering of macromolecular architectures is of utmost importance for designing future materials. Like no other technology, MCRs can help to meet this goal. Recently, the synthesis of sequence-defined macromolecules without the utilization of any protecting group using a Passerini-3CR has been described [32]. Another sequence-specific polymer synthesis with biological applications comprises the peptide nucleic acid (PNA), which is metabolically stable and can recognize DNA and RNA polymers and which can be accomplished by the Ugi-4CR [33]. Yet another application of MCRs in materials science might underscore the potential opportunities to uncover. Ugi molecule-modified stationary phases have been recently introduced to efficiently separate immunoglobulins (Igs) [34]. Currently, more than 300 monoclonal antibodies (mAbs) are moving toward the market. However, the efficient and high-yielding cleaning of the raw fermentation brew is still a holy grail in technical antibody processing. Thus, it is estimated that approximately half of the fermentation yield of mAbs is lost during purification. Ugi-modified stationary phases have been found in this context to be far superior to purification protocols based on natural Ig-binding proteins, which are expensive to produce, labile, unstable, and exhibit lot-to-lot variability.

Fluorescent pharmacophores were discovered by the Groebke–Blackburn–Bienaymè MCR (GBB-3CR) with potential applications as specific imaging probes using a droplet array technique on glass slides [35]. Another group described the discovery of BODIPY dyes for the *in vivo* imaging of phagocytotic macrophages and assembled by MCRs [36].

1.6 Outlook

From the many applied chemistry examples published in the recent literature, it is obvious that MCR chemistry has a bright future. The use of MCRs in property-driven chemistry has just been scratched at the surface. In which areas will be the next applications of MCR chemistry? Will it be in functional materials, imaging, molecular computing, artificial life, "omics" (lipidomics), theragnostics, functional magnetic resonance imaging, or in different upcoming fields? Clearly, the imagination of molecular engineers (*sic chemists*) will determine future directions or as in the saying "Only the sky is the limit."

References

1 Ugi, I., Domling, A., and Horl, W. (1994) Multicomponent reaction in organic chemistry. *Endeavor*, **18** (3), 115.
2 Hulme, C. and Gore, V. (2003) "Multi-component reactions: emerging chemistry in drug discovery" 'from xylocain to crixivan'. *Curr. Med. Chem.*, **1** (10), 51.
3 Domling, A. and Huang, Y. (2010) Piperazine scaffolds via isocyanide based multicomponent reaction. *Synthesis*, (17), 2859.
4 Ugi, I. and Steinbruckner, C. (1960) Concerning a new condensation principle. *Angew. Chem.*, **72**, 267.
5 Bienayme, H. and Bouzid, K. (1998) A new heterocyclic multicomponent reaction for the combinatorial synthesis of fused 3-aminoimidazoles. *Angew. Chem., Int. Ed.*, **37** (16), 2234.
6 Groebcke, K., Weber, L., and Mehlin, F. (1998) Synthesis of imidazo[1,2-*a*] annulated pyridines, pyrazines and pyrimidines by a novel three-component condensation. *Synlett*, (6), 661.
7 Kaïm, L.E., Grimaud, L., and Oble, J. (2005) Phenol Ugi–Smiles systems: strategies for the multicomponent *N*-arylation of primary amines with isocyanides, aldehydes, and phenols. *Angew. Chem., Int. Ed.*, **44** (48), 7961.
8 Sinha, M. *et al.* (2013) Tricycles by a new Ugi variation and Pictet–Spengler reaction in one pot. *Chem. Eur. J.*, **19** (25), 8048.
9 Sinha, M. *et al.* (2013) Various cyclization scaffolds by a truly Ugi 4-CR. *Org. Biomol. Chem.*, **11** (29), 4792.
10 Khoury, K. *et al.* (2012) Efficient assembly of iminodicarboxamides by a "truly" four-component reaction. *Angew. Chem., Int. Ed.*, **51** (41), 10280.
11 Ugi, I. (1982) From isocyanides via four-component condensations to antibiotic syntheses. *Angew. Chem., Int. Ed. Engl.*, **21** (11), 810.
12 Beck, B., Hessa, S., and Doemling, A. (2000) One-pot synthesis and biological evaluation of aspergillamides and analogues. *Bioorg. Med. Chem. Lett.*, **10**, 1701–1705.
13 Fukuyama, T., Robins, B., and Sachleben, R. (1981) Synthetic approach to bicyclomycin: synthesis of the bicyclic system of bicyclomycin. *Tetrahedron Lett.*, **22** (42), 4155.
14 Semple, J.E., Wang, P.C., Lysenko, Z., and Joullié, M.M. (1980) Total synthesis of (+)-furanomycin and stereoisomers. *J. Am. Chem. Soc.*, **102** (25), 7505.
15 Takiguchi, S. *et al.* (2010) Total synthesis of (−)-fructigenine A and (−)-5-*N*-acetylardeemin. *J. Org. Chem.*, **75** (4), 1126.
16 Wan, S. *et al.* (2011) Total syntheses of (−)-fructigenine A and (−)-5-*N*-acetylardeemin: total synthesis and biological evaluation of pederin, psymberin, and highly potent analogs. *J. Am. Chem. Soc.*, **133** (41), 16668.
17 Toure, B. and Hall, D. (2009) Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.*, **109** (9), 4439.
18 Dömling, A., Wang, W., and Wang, K. (2012) Chemistry and biology of multicomponent reactions. *Chem. Rev.*, **112** (6), 3083.
19 Wyatt, P. *et al.* (2005) 2,5-Diketopiperazines as potent and selective oxytocin antagonists. 1. Identification, stereochemistry and initial SAR. *Bioorg. Med. Chem. Lett.*, **10** (15), 2579.
20 Borthwick, A., Davies, D., and Exall, A. (2005) 2,5-Diketopiperazines as potent, selective, and orally bioavailable oxytocin antagonists. 2. Synthesis, chirality, and pharmacokinetics. *J. Med. Chem.*, **48** (22), 6956.
21 Borthwick, A. *et al.* (2006) 2,5-Diketopiperazines as potent, selective, and orally bioavailable oxytocin antagonists. 3. Synthesis, pharmacokinetics, and *in vivo* potency. *J. Med. Chem.*, **49** (14), 4159.
22 Lamberth, C. (2008) Multicomponent reaction in fungicide research: the discovery of mandipropamid. *Bioorg. Med. Chem.*, **16**, 1531.
23 Koes, D. *et al.* (2012) Enabling large-scale design, synthesis and validation of small molecule protein–protein antagonists. *PLoS One*, **7** (3), e32839.
24 Czarna, A. *et al.* (2010) Robust generation of lead compounds for protein–protein

interactions by computational and MCR chemistry: p53/Hdm2 antagonists. *Angew. Chem., Int. Ed.*, **49** (31), 5342.

25 Huang, Y. *et al.* (2012) Exhaustive fluorine scanning towards potent p53–Mdm2 antagonists. *Chem. Med. Chem.*, **7** (1), 49.

26 Bista, M. *et al.* (2013) Transient protein states in designing inhibitors of the MDM2–p53 interaction. *Structure*, **21** (12), 2143.

27 Yan, Y. *et al.* (2004) Inhibition of a mitotic motor protein: where, how, and conformational consequences. *J. Mol. Biol.*, **335** (2), 547.

28 Groebke Zbinden, K. *et al.* (2006) Dose-dependent antithrombotic activity of an orally active tissue factor/factor VIIa inhibitor without concomitant enhancement of bleeding propensity. *Bioorg. Med. Chem. Lett.*, **14** (15), 5357.

29 Pinkerton, A.B. *et al.* (2007) Synthesis and SAR of thiophene containing kinesin spindle protein (KSP) inhibitors. *Bioorg. Med. Chem. Lett.*, **17** (13), 3562.

30 Znabet, A. *et al.* (2010) A highly efficient synthesis of telaprevir by strategic use of biocatalysis and multicomponent reactions. *Chem. Commun.*, **46** (42), 7918–7920.

31 Cao, H., Liu, H., and Dömling, A. (2010) Efficient multicomponent reaction synthesis of the schistosomiasis drug praziquantel. *Chem. Eur. J.*, **16** (41), 12296–12298.

32 Solleder, S. and Meier, M. (2014) Sequence control in polymer chemistry through the Passerini three-component reaction. *Angew. Chem., Int. Ed.*, **53** (3), 711.

33 Chi, K.-Z., Dömling, A., and Barrère, M. (1999) A novel method to highly versatile monomeric PNA building blocks by multicomponent reactions. *Bioorg. Med. Chem. Lett.*, **9** (19), 2871.

34 Haigh, J.M. *et al.* (2009) Affinity ligands for immunoglobulins based on the multicomponent Ugi reaction. *J. Chromatogr. A*, **877**, 1440.

35 Burchak, O. *et al.* (2011) Combinatorial discovery of fluorescent pharmacophores by multicomponent reactions in droplet arrays. *J. Am. Chem. Soc.*, **133** (26), 10058.

36 Vázquez-Romero, A. *et al.* (2013) Multicomponent reactions for *de novo* synthesis of BODIPY probes: *in vivo* imaging of phagocytic macrophages. *J. Am. Chem. Soc.*, **135** (46), 16018.