Innovative multicomponent reactions and their use in medicinal chemistry

Tryfon Zarganis - Tzitzikas

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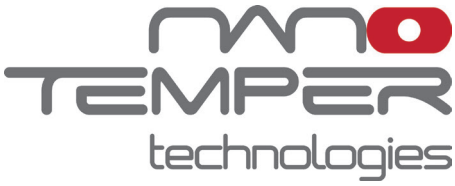

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OUTLINE OF THE THESIS

OUTLOOK

Drug discovery and MCRs

Drug discovery is the process by which new medications are identified. Drug discovery draws upon an integrated set of disciplines that work together to support the myriad activities needed to identify and validate drug targets relevant to a disease, to design or discover probes that elicit a desired pharmacological response from that target and to optimize those probes to provide drug-like candidates that safely and effectively treat the disease.[1]

Drug discovery activities also provide support to clinical research and drug development. Companion diagnostics and PET imaging agents now play an integral role as biomarkers, or measuring drug target engagement, guiding dose selection, diagnosing and characterizing disease states and monitoring treatment effectiveness and progress.[2–4] Imaging agents must be endowed with a specific and specialized collection of biological, physicochemical and ADME properties, which is the inherent specialty practiced by the discovery medicinal chemist.

Working models vary between large pharmaceutical companies, smaller biotech companies, government research groups and academic drug discovery labs, but the general drug discovery process that they all follow is essentially the same (Figure 1).[5,6]

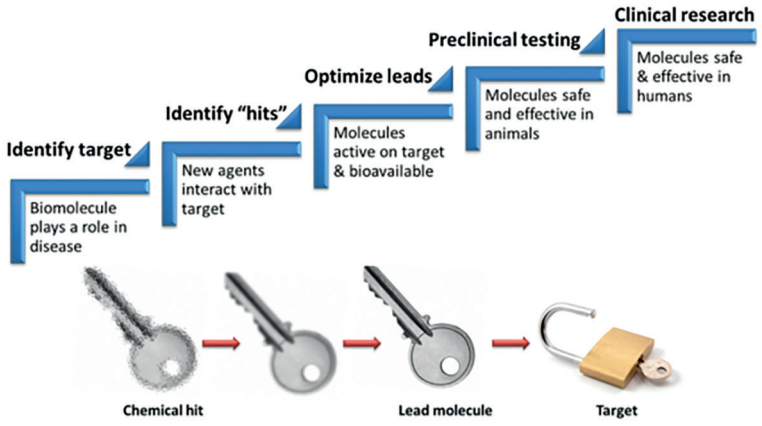

Figure 1. Drug discovery process

It can be easily recognized from figure 1 that the key step in the drug discovery process is the generation of novel chemical entities that can serve as potential drug candidates. Although the use of monoclonal antibodies ('biologicals') as drugs is on the rise, the majority of new drugs are still, and are likely to continue to be, small molecules. In addition successful drug development relies on high efficiency and low cost, and short cycles of design–make–test, and therefore requires short and efficient synthetic sequences for lead discovery. Multicomponent reactions (MCRs) are a unique tool that combines all the above characteristics.[7] They are defined as one-pot processes employing more than two starting materials, for example, 3, 4 even up to 7, where

most of the atoms of the starting materials are incorporated in the final product. Thus, they are atom economic, for example, the majority if not all of the atoms of the starting materials are incorporated in the product; they are efficient, for example, they efficiently yield the product since the product is formed in one-step instead of multiple sequential steps; they are convergent, for example, several starting materials combine in one reaction to form the product; they exhibit a very high bond-forming-index (BFI), for example, several non-hydrogen atom bonds are formed in one synthetic transformation. Therefore MCRs are often a useful alternative to sequential multistep synthesis and ideally are suitable for the generation of libraries of compounds.[8,9]

In **chapter 1**, we discuss all the possibilities that MCR can offer to drug discovery, focusing on how medicinal chemists can use this powerful tool. The MCR derived product can be considered as a synthetic hub to a vast diversity of novel cyclic or acyclic scaffolds by employing different secondary transformations. This "union of MCRs" can serve as a strategy for the rational design of novel MCRs combining two (or more) different types of MCRs in a one-pot process.

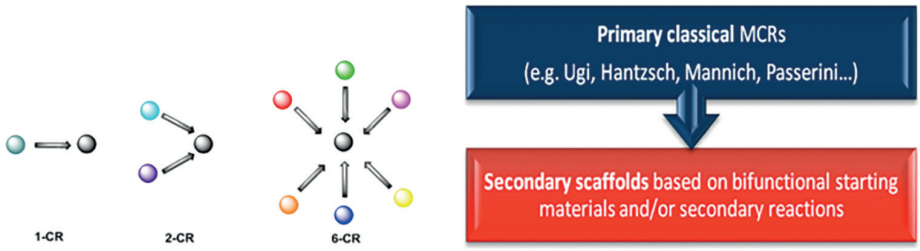

Figure 2. Convergence of Multicomponent reactions

The first step in drug discovery is to identify a biological target whose pharmacological manipulation is expected to impact beneficially on a disease state. The target must be relevant to the disease and druggable. According to a 2006 summary by Overington *et al.*,[10] there are approximately 1500 drugs that have been approved for use in humans (1204 small molecule drugs and 166 biological agents). These drugs work through their actions on 324 unique biological targets. The sequencing of the human genome has had a significant impact in this area.[11] Not only have potential new drug targets been identified but also the complex interaction between biochemical systems is now better understood, allowing researchers to predict potential synergy or redundancy between various systems.

Not all potential drug targets will suitably interact with small molecules or biological agents. When the 3D structure of a target is known but that of its potential binding site is not, computational methods can be employed to suggest likely locations.[12,13] Virtual screening of focused small-molecule or fragment-based libraries can provide additional confidence in a target before a costly high throughput screen is attempted. Wisely, the value of the human insight from experienced structural biologists and medicinal chemists is still apparent in many of these druggability rubrics.[14] Many reviews discuss the hit identification, hit-to-lead, and lead optimization activities associated with drug discovery. Some have represented that process as crafting a key to fit into a

3D lock figure 1. An important aspect that enhances the chances for success is the identification of drug-like scaffolds.[15]

Lipinski's rule of five and its variations still play an important role in triaging and prioritizing potential chemical scaffolds for initiation of structure−activity relationship (SAR) campaigns.[16] The establishment of high-throughput *in vitro* physicochemical and ADME screens and *in silico* ADME have allowed medicinal chemists to prioritize chemical scaffolds and optimize drug-like properties simultaneously with pharmacological activity, thereby identifying structure-property relationships (SPRs) in addition to SARs.[17]

In the next chapters, we describe the design and synthesis of novel scaffolds based on MCRs. In **chapter 2**, the union of MCR concept is exemplified by a concise synthesis of tetrazole-ketopiperazines by two consecutive Ugi reactions. In **chapter 3**, the reinvention and utilization of a known reaction is described in order to access an important chemical entity for most of the MCRs: The isocyanides. A novel isocyanide synthesis from carbonyl compounds and their subsequent application on MCRs without isolating them is discussed proving that IMCRs can be used in a more easy and efficient way. **Chapter 4** describes the synthesis of tri and tetra substituted uracil containing imidazole derivatives via the Ugi-4CR and Passerini-3CR. These compounds were designed with the special in-house software NucleoQuery™ bearing the uracil moiety, giving rise to a library that will be screened in the future against antiviral targets. **Chapter 5** consists of an overview of the synthetic strategies that should be followed to address specific issues rising in many MCRs as the addition to a C=N bond (e.g. Ugi and Passerini reaction) or to a nitrile (e.g. Gewald reaction).

Patent Cliff

The concept of the patent cliff is well-known to anyone with interest in drug development and the pharmaceutical industry. Starting in 2010, a number of blockbuster drugs (originally defined as drugs selling more than $1 billion per year, although $4 to 4.5 billion in annual sales is now considered blockbuster by most big Pharma companies) began losing patent protection (Table 1). Over $68 billion in worldwide sales of branded prescription drugs was lost because of patent expirations and resulting generic competition during the period of 2010-2012,[18] and some estimates suggest that over $290 billion in sales may be at risk for the period of 2012-2018.[19]

The impact on the branded industry, as a whole, is obvious. However, the damage of losing the majority of sales from a blockbuster drug on an individual company can be devastating. Following the expiration of patent coverage on Lipitor (Atorvastatin) in November of 2011, Pfizer lost 59% of its worldwide sales (81% of U.S. sales) in 2012 despite major efforts to maintain those sales and soften the blow from the loss.[20]

Table 1. Blockbuster Drug patent Expirations between 2011 and 2016

Year	Brand Name	2010 sales (billions of dollars)	Company
2011	Actos®	4.6	Takeda
2011	Zyprexa®	5.0	Eli Lilly
2011	Lipitor®	12	Pfizer
2012	Levaquin®	1.4	Janssen
2012	Lexapro®	3.5	Forest
2012	Seroquel®	5.6	AstraZeneca
2012	Plavix®	9.1	BMS/Sanofi
2012	Singulair®	5.4	Merck
2012	Diovan®	6.1	Novartis
2013	Cymbalta®	3.5	Eli Lilly
2013	OxyContin®	2.4	Purdue
2013	Zometa®	1.5	Novartis
2014	Nexium®	5.0	AstraZeneca
2014	Celebrex®	2.7	Pfizer
2014	Sandostatin®	1.3	Novartis
2015	Abilify®	4.6	BMS
2015	Gleevec®	4.3	Novartis
2016	Crestor®	6.1	AstraZeneca

The ever growing structural complexity of modern drugs has led to an increase in the difficulty of synthetic efforts for their production. Of course, MCRs due to its merits, can and already are utilized in the process of industrial drug syntheses. Employing MCRs in the synthesis of drugs can greatly facilitate and shorten the overall production process due to the fast and convergent assembly of target molecules in significantly less steps. **Chapter 6** describes a thorough compilation of the industrial applications of MCRs with illustrating examples. **Chapter 7** specifies one such example i.e. the Telaprevir (Incivek®). It is a member of a class of antiviral drugs known as protease inhibitors which specifically, inhibit the hepatitis C viral enzyme NS3-4A serine protease. It becomes obvious that the introduction of two MCRs, leads to a shortening of the synthesis route by more than 50%.

Another example is Atorvastatin (Lipitor®), a member of the drug class known as statins, which are used primarily as a lipid-lowering agent and for prevention of events associated with cardiovascular disease. It is the best-selling drug in the history of pharmaceuticals, generating $ 120 billion revenues for Pfizer. **Chapter 8** describes for the first time the synthesis of Atorvastatin by MCR chemistry establishing this technology as an effective route towards generics.

Returning to the beginning of this thesis and concluding about drug discovery, the final chapter, **chapter 9**, is dedicated to one of the hottest targets in cancer immunotherapy; The protein-protein interaction (PPI) between PD-1 and its ligand PD-L1. A thorough analysis on the patents of the inhibitors of PD-1 is described demonstrating the importance and future of drug discovery.

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