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Walter Cabri, Lucia Ferrazzano, Alessandra Tolomelli,
Paolo Cantelmi, Tommaso Fantoni
Project for Green Innovation (P4Gi) Lab
Department of Chemistry "Giacomo Ciamician"
Alma Mater Studiorum University of Bologna
walter.cabri@unibo.it

# GREEN CHEMISTRY IMPACT AND EVOLUTION IN THE PHARMA INDUSTRY

***The impact of green chemistry in the pharmaceutical industry is continuously growing thanks to the efforts of academic and industrial research groups. The design of industrial processes inspired by the Twelve Principles of Green Chemistry can be guided by green metrics and nowadays it is relatively simple to stand on the green side when designing the synthesis of a drug.***

## Introduction

During the last decades of the XX century, chemists were able to prove the almost unlimited power of total synthesis [1]. Creativity combined with the development of new methodologies opened a new era, broadening the chemical perimeter in targeting complex chemical architectures. In this context, the segment that gained incredible advantages was the pharmaceutical one, achieving the development of new drugs for unmet clinical need. The technological evolution allowed to explore the molecular space, designing new medicines and contributing to the social wellness.

The synthesis and commercialization of eribulin [2] and trabectedin [3], two molecules inspired by the isolation of natural products from marine organisms, showed the incredible power of total synthesis applied to commercial drug production (Fig. 1). In both cases the available amount from the natural sources was extremely low and a long journey of total synthesis was necessary to bring the drug to patients. Eribulin, with formula $C_{40}H_{59}NO_{11}$, is a simplified structure of halichondrin B possessing 19 stereocenters, while trabectedin ($C_{39}H_{43}N_3O_{11}S$) contains 7 stereocenters. Eribulin was synthetized, by Yoshito Kishi's team at Harvard University in more than 90 steps [4], while trabectedin was synthetized in 46 steps by the 1990 Nobel Prize winner Elias J. Corey, at Massachusetts Institute of Technology [5]. These masterpieces in natural products total synthesis have been the basis for the industrial production of these compounds.

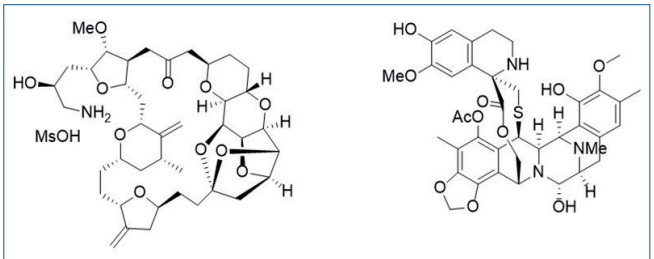



Fig. 1 eribulin trabectedin

Eribulin can be considered the "Mount Everest" of industrial pharmaceutical process chemistry since normally small molecule drugs have shorter synthesis. The availability of complex architectures isolated from natural sources like extraction from plants or fermentation, can consistently shorten the synthesis of the target molecule. In this context, the original 46-steps-synthesis of trabectedin became a 18-steps-one, starting from an intermediate obtained by fermentation, namely cyanosafracin B [5b]. The semi-synthesis remarkably simplified the production of trabectedin and allowed to expand the medicinal chemistry investigation, leading to new analogues as lurbinectedin, that was later developed and brought to the market.

The evolution of drug process design has been influenced by the increasing awareness of the public

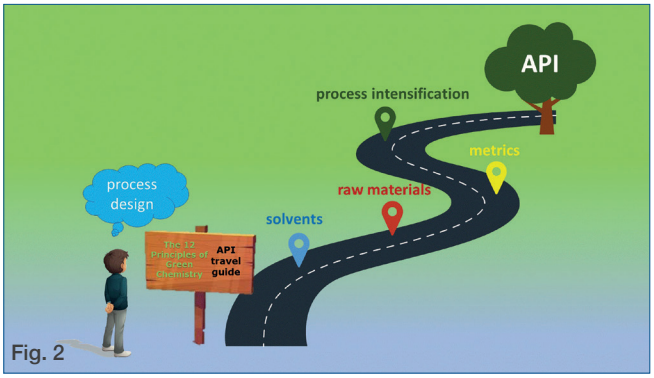


Fig. 2

opinion towards a sustainable society and controlled medicine pricing. Meanwhile, regulatory agencies (Food and Drug Administration, European Medicines Agency, Pharmaceuticals and Medical Devices Agency etc.) issued more stringent guidelines, mainly related to drug safety, and government approved more rigorous laws and control systems for Environmental Health and Safety (EH&S) monitoring. In this context, the introduction of the Twelve Principle of Green Chemistry in 1998 by Warner and Anastas defined the line between benign and malicious chemical synthesis by using "chemical common sense" [6]. The target was inspiring the scientific community to develop a more sustainable approach to chemical transformations. In the last 25 years, the increased awareness and availability of safety data for solvents and auxiliaries, as well as the development of green metrics, powerful catalytic technologies and computing methodologies, allowed to design greener reagents/reactions and multistep syntheses.

Nowadays, it is a matter of choice to stand on the dark or the green side when designing the synthesis of a drug (Fig. 2). We are going to highlight herein which are the main requirements to paint a synthesis with a shade of green.

## Solvents

The greening of industrial processes to preserve the environment and to ensure health and safety for workers has evolved from an ethical approach to an inescapable necessity [7].

The choice of the correct solvents is the most important decision, being them the main source of waste in chemical industrial processes, constituting on average 80-90% of the total process mass [8]. Their selection is critical to guarantee the reaction performances but at the same time to minimize EH&S risks. The American Chemical Society - Green Chemical Institute (ACS-GCI) and several pharmaceutical companies (GlaxoSmithKline, Sanofi, Pfizer, AstraZeneca, etc.) published several similar solvent-selection guides to facilitate the comparison between the most-used solvents and new potentially green candidates (Fig. 3). In particular, these selection guides cover different aspects of greenness such as (i) waste (e.g., recycling, incineration, and volatility), (ii) environmental impact, (iii) health (acute or chronic effects on humans), (iv) flammability and explosivity, (v) stability in handling and storage, and (vi) life cycle assessment (LCA) [9]. Interestingly, most of these guides do not include biogenic solvents like cyrene, γ-valerolactone, hydroxyethyl pyrrolidone or D-limonene

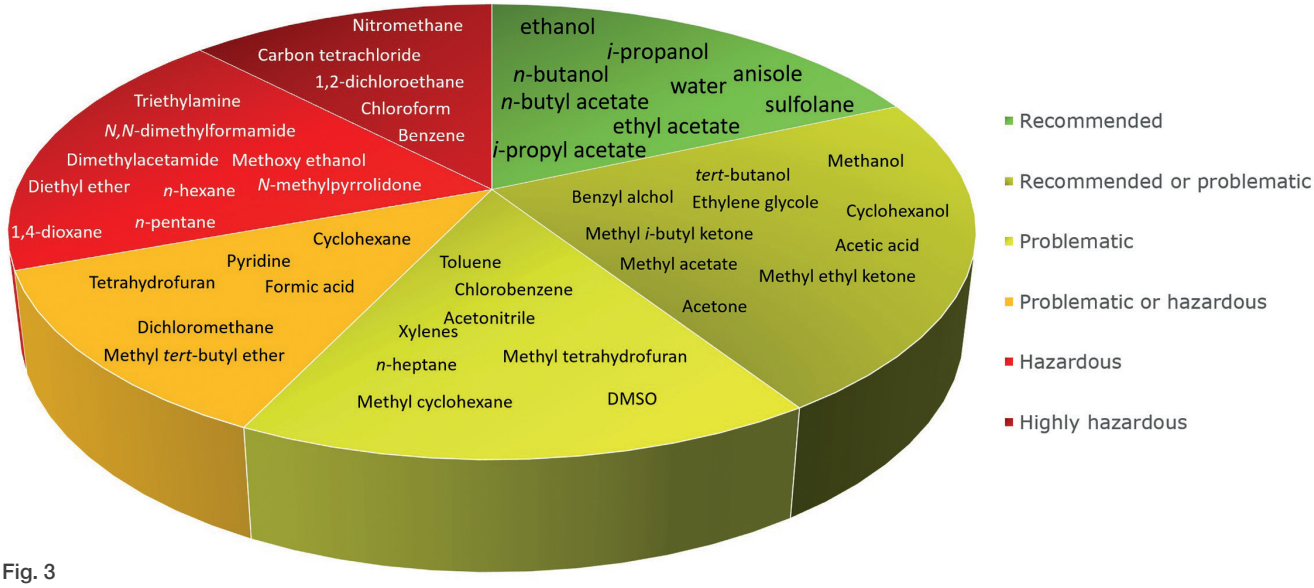


Fig. 3

[10]. These solvents have one main drawback in their high boiling point, that affects their recycling, but their availability and industrial implementation is at the basis of a circular economy approach. Water requires a slightly different discussion. In fact, it is a safe solvent but with some limitations in terms of reactant/reagents solubility and reactivity. In addition, in some countries, it is becoming precious, expensive and the waste treatment that is necessary to eliminate contaminants is a capital-intensive activity. In other words, water plant consumption must be limited as much as possible, since after treatment water is discharged in the environment and not recycled. Sometimes the use of a simple organic solvent that can be easily recycled is more efficient and sustainable.

## Process Design Batch *vs* Flow Chemistry

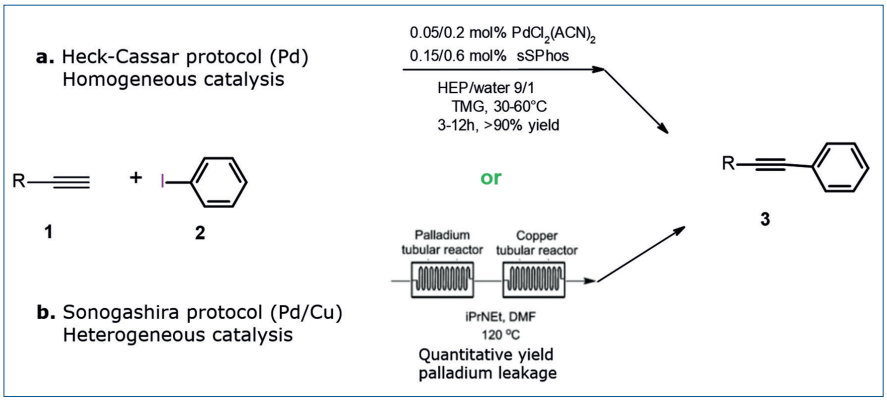
The ultimate goal of process development efforts is to achieve the best process intensity using an easily scalable technology that affords the drug with high quality. Flow chemistry represents an interesting opportunity in this direction. In the early process scouting it is necessary to choose between the development of a batch or a flow approach for the reaction/process design [11]. In this context, the decision diagram to flow chemistry described in The Hitchhiker's Guide to Flow Chemistry is a useful tool that can help the decision-making process [11a]. The use of flow chemistry is the best choice for a large volume product with a relatively short synthesis. However, most of the time the ideal process for the synthesis of an active pharmaceutical ingredient (API) is a combination of batch and continuous/flow reactions. Moving to flow, the target is to reach complete reaction conversions in less than 10-15 min. It is possible to achieve this goal in many ways, such as using highly reactive reagents or increasing temperature, pressure, and concentration to achieve fast transformations.

The green score of a synthesis has to take into consideration a more sophisticated evaluation that, in addition to conversion/yield, efficiency, productivity and raw material consumption, must include energy, maintenance costs, change over procedures and the use of process analytical technologies (PAT). For instance, looking at palladium catalyzed cross coupling reactions, as the Heck-Cassar-Sonogashira, there are two different approaches. In batch reactions, with palladium homogeneous catalysts, it is possible to decrease the amount (0.05-0.2 mol%) of the metal, by adding ligands to expedite the cross coupling in a normal reactor using a green solvent/base mixture. The reaction temperature (30-60 °C) is quite low with long reaction time (3-15 h). Complete recovery of the solvents and the metal can be easily achieved (Scheme 1, pathway a) [12] and the crude product can be isolated with no metal contamination reducing consistently the purification steps. On the other hand, in the flow approach, it is possible to achieve high productivity by using two reactors with two heterogeneous palladium and copper catalysts at 120 °C with non-sustainable solvents and auxiliaries (*i*PrNEt and DMF). The amount of palladium and copper used in the process and the contamination of the final product are directly related to the catalyst leaching (Scheme 1, pathway b) [13]. Not many pharmaceutical intermediates, due to their complex structures, can sustain these extreme conditions.

## Industrial attrition of green projects

The industrial attrition of green projects is the combination of all the elements that hamper the implementation of changes and innovation inside a company [14].

The introduction of new and green processes when the company has already filed the API drug master file or when the entire supply chain is centered on a specific technology has to overcome several barriers. In fact, the classification of a change by the regulatory authorities can determine a long procedure not only for the API drug master file but also for the new drug application (NDA) and abbreviated new drug application (ANDA), implementation and




Scheme 1 - Heck-Cassar-Sonogashira. Batch *vs* Flow

approval [15]. In addition, there is a company's internal resistance to the introduction of innovation, mainly coming from production, logistic and the financial structures.
A typical example is the solid phase peptide synthesis (SPPS) technology that has been optimized for more than 40 years using dimethyl formamide (DMF) as solvent. DMF is the ideal medium for SPPS but, unfortunately, is highly reprotoxic and classified as a substance of very high concern (SVHC) [16]. During the last five years several research groups devoted their efforts to the identification of sustainable alternatives [17]. The industrial implementation of green solvent and their mixtures is sometime difficult, because Technical Operations prefer the DMF reliable technologies and Supply chain/Finance do not want to create turbulences to a well-established raw material management. In addition, the regulatory framework is not well defined and the filing of a process change in a peptide synthesis can trigger additional requests by the regulatory authorities. In fact, this segment of the pharmaceutical industry lacks critical guidelines related to quality, leaving space to reviewers' interpretations [15]. These factors are a serious threat to the introduction of green and innovative processes for peptides production, that is still today one of the main targets of the American Chemical Society - Green Chemistry Institute Round Table [18].

## Green Metrics

Since the introduction in 1992 by Roger Sheldon of the E-factor metric [19], green metrics have consistently evolved. Solvents/reagents/methodologies should be chosen among the more sustainable options in the design stage, then, green metrics like "innovation Green Aspiration Level" [20] can be used by process chemists to guide development.
On the other hand, inside a company, green metrics are a useful tool to overcome the industrial attrition by showing process efficiency to non-chemists. The Process Mass Intensity (PMI), which is directly related to the amount of raw materials that must be purchased to produce one kilogram of product, allows the easy head to head comparison of single steps and overall syntheses (Tab. 1).
The PMI after recovery (PMIr) of solvents and chemicals is an even more precise raw material cost evaluation. A third key metric is the ideality factor (IF) introduced by Baran, that represents a simple way to rapidly measure the efficiency of a synthesis. The closer this value is to 100% the better is the synthesis [21].

| | |
|---|---|
| PMI = | $\frac{\Sigma m(\text{Input materials})}{m(\text{Product})}$ |
| PMIr = | $\frac{\Sigma m(\text{Input materials}) - \Sigma m(\text{recovered materials})}{m(\text{Product})}$ |
| % ideality = | $\frac{\text{No. of construction + of strategic redox reactions}}{\text{total no. of reactions}}$ |

Tab. 1 - Key green metrics for API's process design

## Conclusions

Taking into consideration the large number of green technologies and methodologies, solvents and auxiliaries developed to support greener routes toward API, the identification of a sustainable process with competitive green metrics is only a matter of efforts and investments. Research groups from both Academia and Industry, as well as public investors focused their attention on flow chemistry in order to accelerate the reaction rates and reduce time-consuming productive processes. However, the choice between batch and flow should be dictated by the process green scores and the energy consumption. Energy cost and availability are global issue strongly affected by geopolitical events. In this context, the development of low energy demanding processes is the main challenge that chemists and engineers have to face in the next years.

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## Impatto ed evoluzione della chimica verde nell'industria farmaceutica

L'impatto della chimica verde nell'industria farmaceutica è in continua crescita grazie agli sforzi di gruppi di ricerca accademica e industriale. La progettazione di processi industriali ispirati ai Dodici Principi della Chimica Verde può essere guidata da metriche verdi e, oggigiorno, è relativamente facile pensare in 'verde' quando si progetta la sintesi di un farmaco.