Sustainable Chemistry and Pharmacy 2 (2015) 31–36

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

journal homepage: www.elsevier.com/locate/scp

Putting benign by design into practice-novel concepts for green and sustainable pharmacy: Designing green drug derivatives by non-targeted synthesis and screening for biodegradability

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ARTICLE INFO

Article history:
Received 18 May 2015
Received in revised form
22 July 2015
Accepted 31 July 2015
Available online 21 August 2015

Keywords:
Benign by design
Non-targeted synthesis
Photo-derivatisation
Pharmacy
Chemistry
Green
Sustainable

ABSTRACT

Pharmaceuticals in the environment are an increasing concern, since the improvement of analytical tools has enabled the detection of parent compounds, metabolites and transformation products of a wide range of pharmaceuticals. These micro-pollutants might compromise the water quality and therefore might become a risk for the environment in general and particularly for humans. Major concerns are for example antibiotics. Antibiotics are used to control infections with pathogenic bacteria. Excessive utilization of non-degradable antibiotics by human patients or in farm animals might lead to accumulation in the water compartment and subsequently to the promotion of resistance development when wide areas containing relevant bacteria have sufficient concentrations of active antibiotics leading to a constant selection pressure on the bacteria. Therefore, it would be attractive to develop a new generation of biodegradable antibiotics, which would rapidly disintegrate into innoxious and in the best case inorganic molecules such as water, carbonate, nitrate and alike in sewage treatment plants or surface water. The guiding principle is the "benign by design" concept.

1. Introduction

1.1. Pharmaceuticals in the environment

The active pharmaceutical ingredients (APIs) residues, their metabolites and their transformation products (TPs) resulting from incomplete degradation are often referred as micro-pollutants. They have gained much attention in the scientific community. These and other micro-pollutants are the main cause of the aquatic contamination due to their continuous input into the aquatic ecosystem including sewage flows, surface and groundwater and persistent presence even at low concentrations (ng L^{-1} to μg L^{-1}) (Barceló and Petrovic, 2008; Santos et al., 2010; Michael et al., 2013; Halling-Sørensen et al., 1998; Daughton and Ternes, 1999; Kümmerer and al-Ahmad, 1997; Khetan and Collins, 2007; Kümmerer, 2008). Although present at low concentrations, many of these molecules raise considerable toxicological concerns, particularly as they are present as complex mixtures, making chemical pollution a key environmental problem of our era (Richardson and Ternes, 2014; Trautwein et al., 2014; Brodin et al., 2013; Loos et al., 2013; BIO Intelligence Service, 2013; Kümmerer, 2010; Mompelat et al., 2009; Rockström et al., 2009). Thus, these micro-pollutants are increasingly seen as a challenge to the sustainable management of water resources and a threat to health, water and food safety.

The presence of APIs in the aquatic environment is increasingly seen as one of the major challenges to the sustainable management of water resources worldwide because of expensive and ineffective input prevention measures. The most extensively discussed strategies for the prevention of these micro-pollutants to enter into the aquatic environment are (advanced) treatment processes. However, these treatments have been reported to have their own specific limitations and drawbacks (Kümmerer, 2008; Schwarzenbach et al., 2006; Jones et al., 2007; Wenzel et al., 2008). These technical treatment processes like UV irradiation, ozonation and chlorination can also be responsible for the formation of stable TPs (Hudis, 2007; Joss et al., 2005; Arnold and McNeill, 2007; Boxall, 2009). These TPs can contribute significantly to the risk posed by the parent compound if (a) they are

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http://dx.doi.org/10.1016/j.scp.2015.07.001
2352-5541/

formed with a high yield and (b) they are persistent and/or have high a toxic potential (Fatta-Kassinos et al., 2011; Trovó et al., 2009; Santiago-Morales et al., 2013).

In other words, these advanced treatment procedures should not be considered a general solution to the problem, but as a part of the solution and as well the problem, since some of these treatment processes result in the generation of largely unknown TPs. Often, these treatment processes are not compatible with sustainable development because they focus on the end of pipe solutions linked to the above mentioned problems as well as to increased energy demand.

Also when these micro-pollutants enter into the environment, they are subjected to various abiotic and biotic processes but which may or may not end up in complete transformation or full mineralization. Several national and international studies published in the recent years have confirmed the occurrence of an aggregation of APIs and their persistent and sometime toxic TPs in surface waters (Michael et al., 2013; Ternes et al., 2004; Han et al., 2006; Chang et al., 2008; Miège et al., 2009; Kormos et al., 2011).

Due to the given limited success of end of pipe technologies and the fact that pharmaceuticals even after proper and monitorial consumption finally end up in waste water and surface water as well as in drinking water, it is advantageous to shift the focus to the other strategies i.e. “beginning of the pipe”.

One of the principles of green chemistry is that chemical products should be designed in such a way that their efficacy is preserved while with reduced toxicity and improved biodegradability (Anastas and Warner, 1998). The latter means that to design APIs that can mineralize at a reasonable rate and more or less completely in normal effluent treatment and in the aquatic environment. One building block thereof is the “benign by design” concept (Kümmerer, 2007; Kümmerer, 2012). It is most promising in terms of sustainability and an important building block within green and sustainable pharmacy and chemistry (Kümmerer, 2010). According to this concept, small alterations in the chemical structure of an API may have a significant impact on its activity, solubility and polarity on one hand and on biodegradability on the other hand. Therefore it is reasonable to assume that a set of functionalities exists that can foster both. The approach of designing biodegradable pharmaceutical derivatives is a long-term approach for the sustainable management of the environment i.e. soil and water resources. But developments of such novel designing approaches require time and huge financial support before their full implementation. However, at foremost they need examples demonstrating its feasibility to put the benign by design concept into practice. Methods and opportunities of designing such biodegradable drugs are a challenge that is addressed in the concept presented here.

1.2. Sustainable pharmacy in a nutshell

The goal of sustainable pharmacy is to integrate environmental considerations into drug development, application and disposal in order to minimize environmental risks of applied drugs while retaining or improving pharmacological properties (Kümmerer and Hempel, 2010). The novel field of sustainable pharmacy requires combinations of innovative methods and bridges between different research fields, such as environmental science, pharmacology, drug development, organic chemistry, computational chemistry, analytical chemistry and green chemistry. Improvements along the full life cycle of pharmaceuticals are desirable i.e. from resources to disposal. For the latter, the targeted design of drugs which are readily and fully biodegradable after their introduction into the environment (Kümmerer, 2007). This is an important building block in order to protect water resources and soil from ongoing pollution. Recently, concepts have evolved to integrate the aspect of degradability of drugs after their release into the environment into drug development both in a prospective way into novel lead structures or in a retrospective way into existing pharmaceuticals with problematic environmental properties.

Innovative pharmaceuticals are urgently needed also for medical reasons, for example since pathogenic bacteria are quickly adapting to the new therapies, so that the established antibiotics lose efficacy within a couple of years (Keen and Montforts, 2012). If the innovation process for novel antibiotics is stopped or delayed, dangerous bacterial infections might re-emerge leading to a strong decrease in life expectancy. When a pharmaceutical company sets out to design a molecule for a new application, researchers’ priorities are efficacy and cost. Typically further down the list of priorities if at all on the list, particularly in the pharmaceutical development, is environmental performance. On the other hand, since innovative antibiotics are medically without alternative, environmental aspects because of the frequent utilization are increasingly important for avoiding resistance and for the protection of natural resources such as water and soil. In other words environmentally fully and quickly biodegradable pharmaceuticals are contributing to sustainability in terms of usage and end of life aspects. If they fulfill also the aspects of a green pharmaceutical e.g. the principles of green chemistry e.g. as for their synthesis, they are a striving example how chemical and pharmaceutical science can contribute to sustainability in a far-reaching and impressive manner (Anastas and Warner, 2000). A key to this new understanding is that chemicals and pharmaceuticals do not need to be stable under any circumstances but only where this is necessary (e.g. on the shelf but not in the environment). The different physical–chemical conditions at the different life stages (e.g. pH, redox potential, presence and absence of different types of bacteria, moisture, light etc.) can be exploited to reach this goal.

1.3. Encouraging examples

First promising evidence was found that the goal to combine pharmaceutical development with environmental considerations is feasible by re-structuring the cancer drugs ifosfamide and 5-fluorouracile, which parent compounds are not well degradable (Kümmerer and al-Ahmad, 1997). By adding a glucose moiety to the molecular scaffold of ifosfamide, the biodegradability in the aquatic environment was increased (Pohl et al., 1995; Kümmerer et al., 2000). Not only the glucose was biodegraded as to be expected, but the full molecule. The cytotoxics cytarabine and gemcitabine, which contain (modified) sugar moieties, are much better biodegradable than the structurally related 5-fluorouracile. Of note is that cytarabine is better degradable than gemcitabine as it does not contain fluorine atoms in the sugar moiety (Kümmerer and al-Ahmad, 1997). In all these cases the molecules possess improved biodegradability while – and this is of utmost importance – retaining and even improving the pharmacological properties (Hudis, 2007; Ammons et al., 2007). One resulting drug candidate glufosphamide, i.e. the derivative of ifosfamide, is currently in late stage clinical development (Ciuleanu et al., 2009), whereas cytarabine and gemcitabine are in use since decades (Sneader, 2005). Moreover, a few examples of successful small-molecule-based drugs, which are rapidly degradable in the sewage treatment plant, exist, such as acetylsalicylic acid and valproic acid (Ternes, 1998; Yu et al., 2006). Of note is that these examples of molecules of improved environmental biodegradability were unintended by-products of lead optimization efforts in order to improve drug efficacy rather than being achieved by rational design in order to improve the environmental biodegradability. However, these examples are encouragements that this important goal of sustainable pharmacy will be achievable. Furthermore, some