Sustainable Chemistry and Pharmacy 18 (2020) 100283

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

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

Computational chemistry for green design in chemistry and pharmacy: Building awareness in the classroom

Liliana Mammino

School of Mathematical and Natural Sciences, University of Venda, Thohoyandou, South Africa

ARTICLE INFO

Keywords:
Benign by design
Drug design
Familiarisation with molecules
Green chemistry education
Green pharmacy education
Molecular design

ABSTRACT

Pursuing sustainability requires the design of environmentally benign substances and materials and of sufficiently clean processes for their production, as well as careful attention to their usage throughout their life cycle and to their eventual fate. These requirements have prompted the birth of green chemistry and, more recently, of green pharmacy. The current work focuses on relevant common features of the two areas at educational level. After briefly recalling the reasons that have prompted their birth, and the main objectives of their approaches, it devotes major attention to the design of substances as a tool made increasingly more powerful by the continuous progress of computational chemistry. Particular attention is given to the importance of fostering sound attitudes in approaching molecules and of building awareness of the fundamental roles of conceptual and theoretical knowledge to ensure that the obtained results are meaningful.

1. Introduction

1.1. Green chemistry and green pharmacy education

Acquiring adequate information about green chemistry and green pharmacy is crucial in the professional preparation of both chemists and pharmacists. The importance of green chemistry education has been acknowledged since the earliest stages of the development of green chemistry, by a variety of bodies. For instance, recommendation #7 of the October 1998 OECD Workshop states that

OECD should promote the incorporation of sustainable chemistry into chemical education (within and outside academia) ….

The emphasis on "within and outside academia" is fundamental for any form of education aimed at sustainability, because the dissemination of information needs to reach all types of communities to promote sustainable behaviour patterns. Analogous comprehensiveness is needed for green pharmacy education, where all the stages of a pharmaceutically active compound, from production to distribution, to use, and to disposal, require careful attention and specific approaches. As Anderson et al. (2009) emphasize, pharmacy education

> *refers to the educational design and capacity to develop the workforce for a diversity of settings (e.g. community, hospital, research and development, academia) across varying levels of service provision and competence (e.g. technical support staff, pharmacists and pharmaceutical scientists) and scope of education (e.g. undergraduate, postgraduate, lifelong learning).*

All these aspects are also concerned with the education to sustainability.

The present introduction outlines an ensemble of basic information about green chemistry and green pharmacy, with major attention to the reasons that prompted their births. Section 2 considers an aspect whose importance is continuously increasing within research, both in academia and in the industry – the design of substances having properties that make them sustainable. The section offers an overview of features whose consideration is meant to enhance the quality of the introduction to computer-aided molecular studies in the classroom (including the undergraduate level) by emphasizing the importance of sound conceptual knowledge as a prerequisite to any exercise, research or application.

Overall, the present work implicitly follows a route that could be functional for the presentation of the discourse to learners through a consistent educational pathway. The motivational component entails the information about observed phenomena (impacts of the presence of pollutants in the environment) and the ensuing guidelines aimed at reducing undesirable impacts. These broad-scope aspects provide the background for specific focus on individual guidelines or principles. In the current work, the considered principle is the design of environmentally benign substances and processes.

E-mail address: sasdestria@yahoo.com.

https://doi.org/10.1016/j.scp.2020.100283
Received 6 December 2019; Received in revised form 22 May 2020; Accepted 6 June 2020
Available online 30 September 2020
2352-5541/© 2020 Elsevier B.V. All rights reserved.

1.2. Responses to the challenges of sustainability

Green chemistry and green pharmacy are professional responses to the challenges of sustainability, based on the bodies of knowledge of the two disciplines and promoting research to make their applications increasingly sustainable. Pursuing sustainability requires important changes in a number of aspects, from the modes of production in the industry to everyday life behaviours, including responsible usage of substances and materials. Since any transformation of given substances into others pertains to the domain of chemistry, it is evident that most production activities can be straightforwardly identified as chemical industry or contain relevant chemistry components; even industries whose design and implementation backbones are based on physics, like the construction industry, entail broad chemistry roles in the design and production of the most suitable materials for the purposes of each component of the structure to be built. The criteria and approaches aimed at making chemistry-based production sustainable constitute the core of green chemistry (Anastas and Williamson, 1996; Anastas and Warner, 1998; Tundo and Anastas, 2000) and are summarised through its 12 principles (Anastas and Williamson, 1996).

According to the definition adopted by the IUPAC Working Party on "Synthetic Pathways and Processes on Green Chemistry" (Tundo and Patti, 2001), green chemistry is:

> *the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances.*

The same concepts are expressed in the definition by Anastas and Williamson (1996):

Green chemistry focuses on the design, manufacture and use of chemicals and chemical processes that have little or no pollution potential or environmental risk and are both economically and technologically feasible.

These criteria and objectives extend to the production of pharmaceuticals, as a typically chemistry-based production activity. Green pharmacy is thus viewed as (Green and Sustainable Pharmacy, 2013)

> *the design of pharmaceutical products and processes that eliminate or reduce significantly the use and generation of hazardous substances.*

Toma and Crisan (2018) utilize a more detailed statement, defining green pharmacy as

> *the sum of all measures that should be taken in order to minimize the environmental impact of pharmaceuticals*

and explaining that

> *such measures should be applied during all pharmaceutical activities, from designing new molecules to manufacturing, distribution, dispensing and disposal.*

The prevention of pollution at the source is a declared objective for both areas. It is clearly stated by the first principle of green chemistry (Anastas and Williamson, 1996).

> *Prevention. It is better to prevent waste than to treat or clean up waste after it has been created.*

and definitions of green pharmacy usually include the prevention, or reduction at the source, of those characteristics of substances that have undesirable impacts on the environment, on safety and on health.

Historically, green chemistry was 'born' first among the green sciences, including green pharmacy. Concerns about the undesired effects of the chemical industry on the environment initiated several decades ago and have increased steadily; they regard both the pollution engendered by production processes (whose various forms of wastes have been polluting air, water and soil) and the outcomes of every-day life practices, from the massive combustion of fossil fuels to the careless handling of substances and materials during their useful life and at the end of it. The pollution from production processes was straightforwardly visible from the smokes emitted by industrial chimneys, or the variously-coloured streams flowing from factories into rivers, or the unpleasant smells often surrounding factories. The pollution from every-day life practices was not so immediately visible, but its cumulative effects have become evident in the last decades (the "islands" of plastics in the oceans being one of the most blatant examples). In contexts where chemical industries started comparatively long ago, or where environmental awareness has extensively spread to the public, the adjective "chemical" has become synonym of "non-natural", "potentially toxic" or "potentially polluting" in the public perception (Mammino, 2001); in the last decade of the XX century, the number of young people choosing chemistry for their future profession decreased in several countries, because of the perception that being a chemist implied contributing to pollution (a tendency that could be addressed by green chemistry education (Patti and Scott, 2001)). From the scientists' side, the concerns about environmental pollution prompted the birth of green chemistry. Information about the negative impacts of the chemical species most commonly present as pollutants in the air, water and soil is already broadly spread; it is present in basic and general chemistry textbooks (including those for pre-university instruction) and in a variety of other sources, and, therefore, it is not recalled here.

Green pharmacy developed from the concerns about the pollution resulting from the introduction of pharmaceuticals into the environment. These concerns are much more recent, also because this type of pollution is not as manifestly evident as the pollution engendered by the chemical industry or by the careless handling of substances and materials. The pollution associated with the production of pharmaceuticals is automatically included in the pollution engendered by the chemical industry. At usage level, environmental pollution from pharmaceuticals is partially related to incorrect disposal of unused drugs, but it is also largely inherent in their use, because part of the drugs that enter the human body (or the bodies of animals treated with veterinary drugs) is excreted and enters the environment; some of the drugs' metabolites produced in the body may also be excreted. In principle, water-treatment and sewage-treatment procedures are expected to degrade or eliminate active pharmaceutical compounds to an acceptable risk level (Gruenberg et al., 2017). However, the removal is often insufficient, and the water released from sewage-treatment plants into rivers and lakes often contains pharmaceuticals, thus introducing contamination into aquatic systems (Kaushik and Thomas, 2019). Once in the environment, the drugs are carried by the water circulation, may enter the soil and accumulate in plants (Goldstein et al., 2014; Riemenschneider et al., 2017) and, subsequently, in animals that eat those plants; in this way, they may also enter our food (López-Serna et al., 2013; Riemenschneider et al., 2017) or reach potable water (Calisto and Esteves, 2009; Thomas and Klaper, 2012). By 2018, the presence of 559 active pharmaceutical compounds had already been identified in surface water, groundwater and soil (Toma and Crisan, 2018).

Different types of drugs cause different types of undesirable effects, once they have entered the environment. Antibiotics reach the environment both from human consumption and from the use of veterinary antibiotics to accelerate the growth of animals (Spielmeyer, 2018). The presence of antibiotics in the environment increases the risk that bacteria develop resistance to them (Sandegren, 2019); antibiotic-resistant bacteria would prevent the possibility of treating the infectious diseases that they cause. Psychoactive pharmaceuticals present in the environment may induce genetic effects associated with human neurological disorders, including autism (Kaushik and Thomas, 2019) and may affect the behaviour of some animal species (Gautam et al., 2018). The presence of hormones in water may cause various effects, such as the feminization of male fish due to estrogens (Gruenberg et al., 2017) or sterility in frogs due to progestogens (Gautam et al., 2018).

Like for other types of chemicals, many effects are difficult to predict in advance. It has happened with a number of substances, including cases with large-scale impacts; for instance, when they started been

produced, it was not expected that ClFCs would reach the stratosphere and deplete the ozone layer. It has also happened with pharmaceuticals; for instance, it was not expected that the presence of diclofenac (a non-steroidal anti-inflammatory used to treat livestock) in the environment would cause a sharp decrease in the population of Gyps vultures (Gautam et al., 2018). In addition, it is not easy to predict the combined effects of the simultaneous presence of different drugs in a given environment, which may result from synergies or from interactions between molecules of different drugs (Kolpin et al., 2002). Like for all the chemicals that are not part of the natural environment, the only safe option is avoiding their introduction, persistence and accumulation in the environment.

Because of having developed more recently, information about the negative environmental impacts of pharmaceuticals is not yet so broadly disseminated. It is important that it is disseminated more extensively, to build awareness. Such awareness may also contribute to provide criteria in the selection of chemistry research themes, such as refraining from studies whose results would not be environmentally friendly. For instance, the awareness of the damages ensuing from the presence of antibiotics in the environment would discourage studies such as the investigation of the potentialities of antibiotics for the prevention of metal corrosion (which, if implemented, would increase the presence of antibiotics in the environment).

Practical measures at usage level are crucial for pollution prevention. In the case of chemicals and materials of common use, measures such as garbage collections separating different types of wastes and facilitating recycling have proved highly effective. Recent recommendations for pharmaceuticals comprise the practice of returning unused medications, so that they can be utilised by other patients (Bekker, 2018), limiting prescriptions to the cases where the medication is really expected to benefit a patient (Bijl, 2019), or improving the efficacy of water and sewage treatment (Kümmerer, 2019). However, the most effective approach, both for other chemicals and for pharmaceuticals, would be the design of substances (or drugs) that, besides having the desired properties (or the desired pharmaceutical properties), also have properties making them environmentally benign. For pharmaceuticals, this design would target the pharmaceutical properties themselves, with objectives such as being effective with lower doses (e.g. if the potency of individual molecules is enhanced through suitable substituents, or if a greater proportion of molecules reaches their biological targets) or maintaining good activity levels for a longer period (having a longer useful life before expiry). The green chemistry principle “design for degradation” (principle 10) ought to apply also to pharmaceuticals; it would comprise biodegradability (Toma and Crisan, 2018) as well as the design “for fast and complete environmental mineralization after their excretion” (Kümmerer, 2019), so that the molecules do not remain active after entering the environment. In summary, the design of pharmaceuticals (like the design of any other chemical) needs to consider their entire life-cycle, from their production to their use and to their disposal, and their environmental impacts in each of these stages (Gualtero, 2005; Kralish et al, 2015; Emara et al, 2018; Kümmerer, 2019).

For the production component, green pharmacy, like green chemistry, implies the design of more environmentally-friendly production processes to replace less friendly ones (e.g., Inayat et al., 2018). The criteria are expressed by the 12 principles of green chemistry.

2. The design of benign substances – a key concept of green chemistry and green pharmacy

2.1. Similarities of objectives in green chemistry and green pharmacy

Pharmacy research and chemistry research have broad overlaps, because chemical knowledge is at the basis of pharmaceutical research and because questions arising in one of the two areas are often significant also for the other. At educational level, the interfaces can be rooted in the nature of the two disciplines. Chemistry is the science of substances; it studies their properties and their transformations, and interprets them by studying molecules, their properties and their behaviours; it continuously designs new substances to meet specific needs in improved ways. The main objective of pharmaceutical research is the design of substances that can have desired effects on our organism, in order to treat diseases or to enhance our wellbeing; therefore, it also needs to study the properties and behaviour of their molecules.

Both green chemistry and green pharmacy aim at preventing environmental contamination by avoiding the introduction of pollutants into the environment. This requires avoiding the production of substances that can be harmful, and also avoiding the generation of pollution during their production processes.

The design concept is a key concept in the definitions of both green chemistry and green pharmacy: design of environmentally benign new substances to replace currently used ones that are not sufficiently benign; and design of production processes that reduce wastes, reduce the production of hazardous substances (including hazardous intermediates, so that a process is inherently safe), reduce energy consumption, and maximise the extent to which starting materials are transformed into desired products (atom economy). In turn, the design of sustainable processes largely relies on the design of substances that can play important roles in making a process greener, such as catalysts with specific actions. The ‘benign-by-design’ concept was introduced since the early stages of green chemistry (Anastas, 1994) and has developed into one of its major pillars (Meurig et al, 2001; Kümmerer, 2007; Gawande et al., 2013).

2.2. Designing molecules and predicting their properties

The design of new substances and the design of new drugs have been the main undertaking of chemistry and pharmacy through many centuries (actually, in the Renaissance period and through the XVI century, the design of medical remedies was viewed as the main task of both alchemy and incipient chemistry). Up to few decades ago, the design of substances has been an exclusively experimental task, proceeding through trials until a substance with the desired properties was obtained. In recent decades, the design relies more and more extensively on the information obtainable through computational chemistry. The pharmaceutical industry is actually the industry that has been making the most extensive and refined use of computational chemistry (computer-aided drug design) because of the need of extremely fine tuning of the properties of drugs to maximise their therapeutic benefits and minimize undesired side effects in the body. The recent recognition of the polluting effects of the presence of pharmaceuticals in the environment demands attention to additional aspects in their design and, therefore, requires research for the development of corresponding approaches.

The roles of computational chemistry in making chemical production and pharmaceutical production greener offer an important and potentialities-rich overlap area for the two disciplines, both at research level and at education level. Selected major features of possible interfaces between green chemistry and computational chemistry at educational level have been outlined in (Mammino, 2018). Because of the function of drugs, their design requires extremely careful attention to their properties. On the other hand, all the considerations relevant for the design of pharmaceuticals are also relevant for the design of other chemicals; furthermore, the design of other chemicals (Computer-Aided Molecular Design, CADM (Austin et al., 2016-a)) can improve through extensive incorporation of the careful attention to the finest properties of molecules that is typical of drug design.

The properties of substances depend on the properties of their molecules. The more we know and understand about the properties of a molecule, the better we can understand the properties and behaviour of that substance. When a substance has not yet been synthesised, studying the properties of its molecules enables predictions of the properties of

that substance sufficiently reliable to enable informed decisions as to whether synthesizing and testing it may be potentially interesting or totally uninteresting. This also has economic relevance, as it enables enormous cost-saving for the experimental components, by enabling it to focus on the more promising options. The most relevant aspect of pharmaceuticals is their biological activity; therefore, one searches for relationships between the molecular properties and the activity using a regression-type equation (QSAR, Quantitative Structure Activity Relationships). Other substances may be interesting for a variety of physical or chemical properties; therefore, the search for relationships focuses on the property that is mostly desired from a given substance (QSPR, Quantitative Structure Property Relationships). QSAR is mostly used for activities on living beings, which comprises pharmaceuticals (Verma et al., 2010) but also other substances with such activities, like pesticides (Raimondo and Barron, 2020; Villaverde et al., 2020). QSPR is used for properties typical of the other areas of the chemical industry, such as the catalytic action of a catalyst (Begum and Raju Achary, 2018) and specifically for properties that are relevant in a green chemistry perspective (Papa and Gramatica, 2010; Fayet and Rotureau, 2016), The modelling approaches in the two methods are analogous (Chtita et al., 2016). Most of the molecular properties (descriptors) utilised in QSAR or QSPR are obtained through quantum chemistry calculations, i.e., through the computational study of molecules.

2.3. Familiarisation with molecules in the classroom

2.3.1. Necessity of extensive familiarisation with molecules

In the last three decades, exercises and projects involving the use of selected computational chemistry techniques have been introduced into undergraduate programs in several institutions and countries, from early experiments (e.g., Gillom, 1989; Canales et al., 1992; Casanova, 1993; Delaware and Fountain, 1996) to specific uses in more specialised courses (e.g., Thompson and Sears, 2005; Miller et al., 2019). Some experiments have also extended to the secondary school level, involving both pupils and teachers, also through teacher training projects (Lundell and Aksela, 2003; Aksela and Lundell, 2008; Ochterski, 2014). Currently, the most frequent objective at university level is that of familiarising students with the use of software relevant to the content of a given course. The main objective in the early initiatives, as well as in the trials with secondary school pupils, was that of familiarising learners with molecules. A review and analysis of these initiatives would however go beyond the scope of the current work.

Recurrent phenomena in recent years highlight the importance of extensive familiarisation with molecules as pre-requisite to the use of computational software for more advanced purposes. The situation described by Goerigk and Mehta (2019) for the selection of Density Functional Theory (DFT) calculation methods is true for many other areas or forms of computational chemistry applications. Computational techniques are not used only by specialists in computational and theoretical chemistry, because their accessibility in commercial software prompts their use by many; on the other hand, chemically-uninformed or theoretically-uninformed use can lead to difficulties in the interpretation of the obtained results, and also to subsequent utilisations of results that are not sufficiently founded to enable conclusions or to be transferred to practical applications. Through professional activities related to academic and research work, the author has encountered a number of cases where otherwise valid (technically correct) computational studies are performed on totally unsuitable geometries of the molecules considered, as well as cases in which researchers utilize computational software with a totally black-box approach and then experience difficulties in understanding and interpreting the obtained results. Preventing such situations would require sufficiently detailed theoretical preparation to enable appropriate awareness of the nature of the selected computational approaches and of the nature and meaning of the obtained results. On the other hand, the acquisition of adequate theoretical knowledge requires levels of mathematics mastery that are not always present. It becomes important to convey qualitative information in a sufficiently rigorous and accessible way to build awareness about how to approach computational work, even when the mathematics remains a 'black-box' component. An attempt to outline essential concepts in a qualitative way is currently 'under construction' by the author.

The next subsections devote specific attention to the fostering of sound attitudes in the way of looking at molecules as necessary prerequisite to any other activity concerning molecules. The features considered are suitable for within-the-classroom work at the undergraduate level of both chemistry and pharmacy courses (and, with suitable adaptations, may be extendible to the higher secondary school level). The outlined approaches, and the information about students' responses, are related to the author's direct experience: teaching the quantum chemistry course (a course in the intermediate year following the triennial B.Sc. degree, which might be viewed as equivalent to a fourth year course) at the University of Venda for the last 22 years, and also being involved in some initiatives to familiarise students with computational chemistry in other contexts (including a couple of presentations in secondary schools). The author uses interactive teaching and integrates teaching and educational research in an action-research perspective (Levin, 1947), with the three recursive components of planning that involves reconnaissance, taking actions, and fact-finding about the results of the action (Levin, 1947; reported in Girod). In this way, all the activities pertaining to a course constitute 'experimental' sources of information about students' perceptions, the difficulties they encounter, and their responses to pedagogical explorations aimed at addressing diagnosed difficulties (Mammino, 2016, 2019). Furthermore, information from other sources (e.g., from conference presentations by young researchers) also constitutes valuable pedagogical information, highlighting the need to take care of specific aspects in the training of young specialists.

2.3.2. Molecules as three-dimensional objects

A paramount advantage offered by the development of molecular visualization software is the possibility of visualizing molecules as 3-dimensional entities. This is essential to familiarise students with more complete images of molecules than those associated with structural formulas (whose functions are in any case essential and not replaceable) or other 2-D representations, adding new insights. It is also crucial for learners to overcome the perceptions prompted by obsolete pre-Bohr-type images, still encountered in various contexts despite warnings from chemistry educators, and leading to the inference that molecules are flat (the images in question are those showing circular orbits around each nucleus and electron pairs shared between touching orbits; various students in different years have indicated those images to the author as 'proofs' that molecules are flat, with what is actually a logical inference from an incorrect image).

It may be relevant to note that the familiarisation with 3-D structures can make enormous difference not only in students' perceptions and understanding, but also at research level. Once the habit is acquired, it becomes a spontaneous habit in any approach to molecules, even by simply looking at structural formulas. For instance, the habit to consider molecules as 3-D objects has enabled the realization that the quinine molecule can form an intramolecular hydrogen bond (Fig. 1.; Bilonda and Mammino, 2017). On the other hand, the author has encountered posters presented at conferences, showing results of works such as the study of the interactions of a certain molecule with selected solvents, or with other molecules, where only high energy conformers of the given molecule were considered, or docking studies where only high energy conformers of a drug molecule were docked into a protein. The utilised high-energy conformers had geometries straightforwardly replicating the structural formula of the molecules, without attention to the actuality of 3-D geometries and to the intramolecular interactions that determine energetics. On more than one occasion, the author has engaged young presenters in discussions aimed at guiding them through

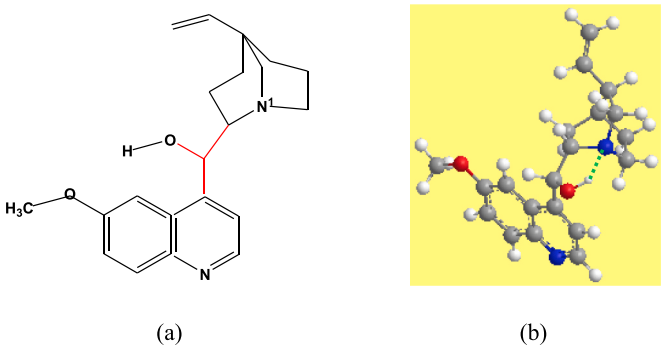

Fig. 1. Structural formula of the quinine molecule (a) and 3-D structure (b) of a conformer having an O–H···N intramolecular hydrogen bond (green dotted segment). On looking at the structural formula, one needs to imagine the rotation about the bonds denoted by red segments to realise the possibility of the IHB. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the analysis of the possible geometries of the given molecule, and which geometries may be more 'comfortable' and, therefore, preferred, for the molecule. It was surprising to realise that even close-to-completion PhD students presenting results of that type were not aware of the importance of a preliminary conformational analysis of their molecules, and were also unaware of how to identify possible intramolecular interactions and possible different geometries. Occurrences like these stress the importance that thorough familiarisation with molecules precedes the utilisation of computational techniques for research purposes.

The first step of the familiarisation with molecules as 3-D objects involves the rotation of the visualised structures in space, to have a 'good look' at them from all the sides. The second (more advanced) step involves the recognition of possible intramolecular interactions, which are relevant to try and guess the best geometries for the given molecule. The most important of such interactions (and also the easiest to recognise in a 3-D structure) are intramolecular hydrogen bonds (IHBs). Within the familiarisation-with-molecules process, students are invited to recognise potential donors or acceptors and, subsequently, to check whether they can – by rotating single bonds – be brought to mutual distances and orientations enabling the formation of IHBs. It is preferable to start from simple examples (like the one shown in the first images in Fig. 2), where the recognition of the possible IHB is immediate; then, molecules with more complex structures, or with the possibility of more than one simultaneous IHB, can be proposed. Weaker IHBs (such as O–H···π IHBs, last image in Fig. 2) can also be included, because of their significant stabilizing effects. The examples to propose to students can be easily derived from the molecules that are objects of investigation by the lecturer, as is the case of the examples in Fig. 2, which were among those utilised by the author.

Molecules which can form one or more IHB are also the most suitable for a first introduction of the relative energy concept, because of the frequently considerable energy difference between conformers having a given IHB and conformers from which it is absent (for instance, the conformer denoted as a′ in Fig. 2 has considerably higher energy than the conformer denoted as a). Once the possible IHBs in a given molecule have been recognised, optimization can be performed at simple computational levels, considering both the geometry with a given IHB and the geometry without it; then, the energies are compared, and populations calculated. This makes it easy to explain that, if one wants to understand the behaviour of the given molecule in specific circumstances (for instance, its interactions with a solvent), one would first of all consider the conformer with the IHB, as the one present in greater proportion and, therefore, determining the behaviour of the molecule. Since we do not know a priori the fate of IHBs in solutions with solvents which can form H-bonds with the solute molecule, it is interesting to study both conformers in solution. On the other hand, considering only the high energy conformers and not the low energy ones would make the results meaningless.

These exercises are functional to build the awareness that a conformational study is pre-requisite to any other study concerning a given molecule, including its interactions with a solvent, with another molecular species or with a biological target. An illustrative example is shown in Fig. 3, considering caespitate, an acylphloroglucinol with antituberculosis activity (Mathegka et al., 2000). The figure shows the geometries of four of its conformers; the numbers in the first row under the images are the relative energies (kcal/mol) of those conformers in vacuo, and the numbers in the second row are their relative energies in water solution (Mammino and Kabanda, 2012). The first three conformers have sufficiently low relative energies in at least one of the two media (vacuum and water), so, they can be considered as potential responsibles of the biological activity and utilised for further investigations; the relative energy of the fourth conformer is too high for it to have sufficient population to exert significant biological activity. It is also important to stress that, while utilising all the four conformers in further studies (e.g., docking with a protein) would not constitute an error (just a waste of time for the highest energy one), not including the first three conformers would be an error devoiding the results of meaning. Furthermore, the energy values stress the importance of taking solvent effects into consideration: the second and third conformers would not be considered interesting on the basis of the results in vacuo, but the results in water solution show that they might actually be the ones responsible for the biological activity or contribute to it.

Understanding and internalising the concept that the low energy conformers are the conformers responsible for the behaviour of a substance (including its biological activity) appears to be challenging for many students. Although the author mostly refrains from using analogies (unless they can be built in a conceptually rigorous way), in this case

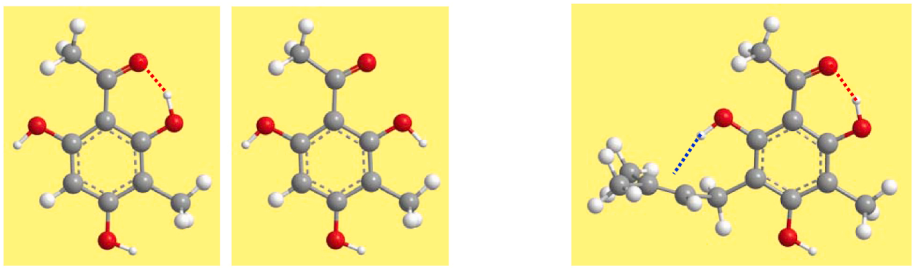

Fig. 2. Recognition of intramolecular hydrogen bonds through simple examples. The first two images illustrate a geometry analysis focusing on the possibility of formation of an intramolecular hydrogen bond (IHB): both the geometry with the IHB (a) and without the IHB (a′) are utilised as inputs, to emphasize the energy difference between the two conformers (optimization will also rotate the acyl group in a′, so that its sp^2 O is further away from the O atom of the OH group). Image b shows a case where two different IHBs are present in the same molecule, the O–H···O IHB (red dotted segment) and the O–H···π IHB (indicated by a blue dotted segment in the general direction of the double bond in the prenyl chain). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

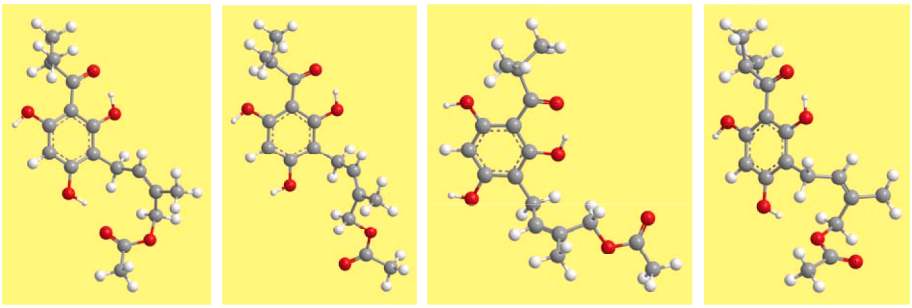

Fig. 3. Optimised geometries of four conformers of caespitate (Mammino and Kabanda, 2012). The first value under each image is the conformer's relative energy (kcal/mol) in vacuo, the second value is its relative energy in water solution.

she frequently resorts to an anthropomorphic analogy which appears to be suitable to stimulate some responses. The different 'geometries' (positions and corresponding arrangements of limbs) of the human body are taken as the conceptually analogous of different molecular geometries. A human being can be standing, or sitting, or lying down, but can also take a variety of more difficult 'geometries', such as standing on one leg, or standing with the arms up, etc. Students are asked which 'geometries' are more comfortable for us, and guided to the conclusion that these are our preferred 'geometries'. These are also 'geometries' that require less effort from our side. Similarly, the preferred geometries of a molecule are those corresponding to lower energy. In an ensemble of many persons, most people will be sitting or standing (at least, during day time); only very few, or none, will take the more effort-demanding 'geometries'. Similarly, in an ensemble of molecules, most molecules will take the low-energy geometries, with only few taking the high energy ones. Then, if, for instance, we consider the interaction of a drug with its biological target, we need to consider that there will be too few molecules with high-energy geometry to have a significant role and to reach biological targets. The activity of that drug in the body is determined by the molecules with preferred geometries, as they are present in much greater number and, therefore, can 'do' something that has an impact. Familiarity with mathematics is of great help in this regard; however, it is necessary to explicitly guide students to realise that, e.g., a population expressed by a number followed by a very small power of 10 (10^{-10}, 10^{-15}, etc) expresses a population that is too small for the corresponding conformer to be able to 'do' something that is not negligible and, therefore, those conformers can be neglected in the study of interactions with biological targets. It may be added that references to the study of the interactions of a molecule with a solvent, or with a biological target, are suitable since the early stages of familiarisation with molecules, even if the students will not perform those type of studies, because they contribute to build the awareness of the variety of issues that can be considered when studying molecules and their behaviours.

2.3.3. *The properties of molecules*

Some properties of molecules can be analysed easily once the optimised geometries are obtained from calculations. In the last 22 years, the author has invited the students taking the quantum chemistry course at the University of Venda to calculate selected molecules and analyse their geometric properties. This involved the consideration of bond lengths, bond angles and dihedral angles, and their analysis in terms of what students already knew from undergraduate courses. For instance, in one of the exercises, each student was given a not-too-small hydrocarbon molecule and asked to calculate it at the AM1 level, and also to calculate a certain number of derivatives with halogen atoms in turn replacing one or more H atoms. Students were then asked to prepare tables with the optimised geometric parameters (which can be straightforwardly taken from the outputs) and to compare and discuss the values. This involved the consideration of questions such as:

- Why certain bonds are longer and others are shorter. The recommended derivatives were particularly useful because halogens (as substituents) are ideal to highlight the effect of the size of atoms on the bond length.
- Why the C–C bond in benzene is shorter than a single C–C bond and longer than a C═C double bond.
- How the features of the optimised geometries (bond angles, dihedral angles) relate to what students already knew about the hybridisation of atomic orbitals.

Although students were familiar with concepts such as hybridisation of atomic orbitals, or multiple bonds, or aromaticity of the benzene ring, applying the concepts to 3-D images, which actually show the spatial geometry, or to the analysis of numerical values, was like entering a totally new perspective.

Optimization outputs contain a variety of other information that can be utilised for comparative analyses of properties of molecules with which students are already familiar. An example is the dipole moment. Students know that molecules can be more or less polar, and comparing dipole moments makes the concept more concrete. The scope may be broadened by recalling that it may have additional relevance for specific classes of compounds; for instance, the dipole moment enables the identification of anthracyclines which may have anticancer activity, as only those whose dipole moment falls within a certain range have this activity (Bushelyev and Stepanov, 1989).

Other molecular properties may be introduced in a qualitative way. For instance, showing the shapes of molecular orbitals offers additional views of the complexity of molecules (they can be shown also at undergraduate level, before students encounter quantum chemistry, by introducing the simple information that molecules have molecular orbitals just as atoms have atomic orbitals). Molecular vibrations are another aspect that can be shown qualitatively, and proves quite impressive when students encounter it for the first time. In her courses, the author did not ask students to calculate frequencies, but calculated the frequencies of selected molecules with increasing sizes and visualised the vibrations for students. It was considered important to foster the perception that molecules are not rigid objects. Showing the vibrations was also related to the student' previously acquired knowledge by informing them that those vibrations are at the origin of the signals in the IR spectra, with which they had familiarised in undergraduate organic chemistry courses without knowing their origin.

2.4. *Qualitative information about what can be obtained from computational work*

It is possible to build preliminary awareness of selected investigation questions and relevant outcomes from computational work even before students actually learn how to obtain them, by providing qualitative information about them and about their relationships with different

types of investigation. These expansions-of-scope appear to engender keen responses from students, likely because they go beyond the confines of the specific course and offer broader views on what can be done within chemistry, on the bases of the knowledge acquired in the given course.

The drug design concept is often quite attractive for chemistry students (and obviously motivating for pharmacy students), and information related to it is received with interest. It comprises the case of the relative energies of the conformers and how they indicate which conformer/s can be viewed as potentially responsible for a given property or a given biological activity, outlined in the previous section, and it can be extended to a number of other issues.

As already mentioned, talking about biological activities offers a good opportunity for the introduction of the importance of solvent effects. Although students are usually not asked to perform calculations in solution in the early stages of their approach to molecules, qualitative information may be sufficient to highlight the main terms of the question. Drugs exert their activity within the body; therefore, they exert it within a medium. This means that it is necessary to study the behaviour of a drug's molecule in a medium (Mammino and Kabanda, 2014). Water is the main medium in living organisms and, therefore, it has always to be considered; it is also advisable to consider a non-polar solvent to mimic non-polar media (such as the lipid phase) in the organism, above all for molecules whose solubility in water is poor. When considering the interaction of an active drug with a protein, it is important to consider the geometry that the drug will have in the medium where the drug and the protein are preferably present in the body (aqueous or non-polar), because this would offer the closest correspondence to the actual situation within the body. Similarly, considering the medium is important in the design of industrial chemical processes that occur in solution (Austin et al., 2016-b).

Cases like the one shown in Fig. 3 provide key examples of the importance of solvent effects, as the energy values highlight nearly dramatic effects of the solvent on the molecule's conformational preferences: the solvent shifts the conformational preference to conformers not containing the weaker IHB closing the larger (11-member) ring. The information may be conveyed in a more convincing way by adding images of adducts with explicit water molecules, which the lecturer calculates separately, and which show water molecules inserted in the space where that IHB was present, and H-bonded to the donor and the acceptor of that IHB (Mammino and Kabanda, 2008). Even the concept of the competition between intra and intermolecular hydrogen bonding in solvents capable of forming H-bonds can be introduced qualitatively with reference to these images. For instance, images and relative energies (Fig. 3) show that, in the case of caespitate, the IHB closing the 6-member ring 'wins' the competition with the solvent, whereas the IHB closing the 11-member ring 'loses' the competition.

The issue of the mechanism through which a certain pharmaceutical exerts its activity can also preliminarily be presented qualitatively, through images. It is the case of the interaction of a drug with the active site of a protein, or the case of DNA intercalation, which prevents its unravelling and, therefore, its duplication. The latter is also the way in which, e.g., anthracyclines exert their anticancer activity, and qualitative information is adequate to convey the importance of the presence of a flat rigid part in the drug for good intercalation.

Some information may be perceived as more relevant, and more of interest to students, according to the context. For instance, students respond with keen interest to information about mechanisms of antimalarial activities in contexts where malaria is present/endemic. Different antimalarials act with different mechanisms: interaction with proteins of the *plasmodium* (the protozoan parasite responsible for malaria), intercalation with its DNA, and also modification of the environment, making it unfavourable to the parasite (for instance, the pyrimethamine-sulphonamide combinations exerted antimalarial activity by lowering the level of folic acid, because this prevents the parasite from polymerising the heme after consuming the haemoglobin, and the failure of heme polymerisation is fatal for the parasite).

New areas where chemistry and pharmacy encounter extensive synergies can also be introduced at qualitative level, and the associated images can be particularly fascinating. It is the case of the design of suitable cavity-containing molecular systems for drug delivery within the body. In such cases, the drug molecule is host to the deliverer, usually a nanoparticle. The nanoparticle may protect the drug molecule from degradation in the body, facilitate its controlled release, help increase the proportion of drug molecules that reach their biological target, and also help reduce undesired effects; in some cases, the deliverer may also enhance the performance of the drug by favouring its action (Pandey and Dahiya, 2016; Guérineau et al., 2019). Of course, the deliverer itself should not have polluting effects once excreted. A possibly benign option could be that of building nanoparticles from naturally occurring multi-units molecular structures with easy open–closed structural transformation (a computational investigation of the properties of cavity-containing molecular structures built from naturally occurring acylphloroglucinols is currently in progress (Mammino, 2017, 2020) and students find the images fascinating).

3. Discussion and conclusions

Green chemistry is the chemists' response to the needs of sustainability; similarly, green pharmacy is the response to these needs by the bodies and specialists involved in the production and utilisation of pharmaceuticals. Both areas entail crucial education components, both in terms of education for the general public (to prepare informed citizens) and in terms of the preparation of specialists capable of meeting the challenges inherent in the design of environmentally-benign substances and pharmaceuticals. Research in green chemistry education has grown steadily in the last two decades, and green chemistry components have already been extensively incorporated into chemistry education in a number of countries. Research in green pharmacy education is comparatively new; it is expected to grow rapidly, and it has already started involving pharmaceutical companies (Summerton et al., 2016).

Many approaches developed for green chemistry education can be adopted by green pharmacy education. Learners' active involvement can be viewed as one of the crucial aspects, because active involvement maximises the convincing abilities of instruction (Mammino, 2015). For instance, learners can be invited to search information about the effects of pharmaceuticals in the environment in an independent manner, as literature search projects which can be run along the lines utilised by the author for the introduction of information about green chemistry within a process technology course (Mammino, 2015). Analogous projects can involve the search for qualitative information about issues that will be encountered more in detail at later stages of the students' career, such as drug-target interactions, to expand students' mental pictures about molecules, what they can do and what we are interested in studying, since their initial familiarisation with molecules.

The design of environmentally benign substances is at the core of both green chemistry and green pharmacy. Rational design relies largely on computational chemistry. The familiarisation (since the undergraduate level) of chemistry and pharmacy students with the potentialities of computational approaches would contribute to prepare researchers and professionals equipped with knowledge that is fundamental to pursue sustainability, whether through direct involvement in computational research or through collaboration between experimental and computational chemists or pharmacists.

The largest part of this work has focused on the importance of building awareness that is fundamental for sound utilisation of computational techniques: awareness about how to approach the study of molecules and awareness about the types of information that can be obtained through computational studies. They both entail building familiarity with molecules. The former is fundamental to perform meaningful computational research; the latter is fundamental both for the design of computational research and for the collaboration between

computational and experimental scientists. Qualitative information, supported by visualization, proves valuable to initialise the building of such awareness since early stages of students' careers, well before they may become acquainted with computational techniques. The awareness engenders an attitude platform ensuring correctness of investigation approaches and availability to synergy between experimental and computational research. Such platform is crucial for the design of benign-by-design new chemical species and new pharmaceuticals.

Note

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Liliana Mammino: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Resources, Software.

Declaration of competing interest

The author declares that she has no competing interests.

References

Aksela, M., Lundell, J., 2008. Computer-based molecular modelling: Finnish school teachers' experiences and views. Chem. Educ. Res. Pract. 9, 301–308.

Anastas, P.T., 1994. Benign by design chemistry. In: Benign by Design. American Chemical Society, Washington, pp. 2–22.

Anastas, P.T., Williamson, T., 1996. In: Anastas, P.T., Williamson, T. (Eds.), Green Chemistry. American Chemical Society, Washington.

Anastas, P.T., Warner, J.C., 1998. Green Chemistry: Theory and Practice. Oxford University Press, New York.

Anderson, C., Bates, I., Beck, D., Penick Brock, T., Futter, B., Mercer, H., Rouse, M., Whitmarsh, S., Wuliji, T., Yonemura, A., 2009. The WHO UNESCO FIP pharmacy education taskforce. Hum. Resour. Health 7, 45. https://doi.org/10.1186/1478-4491-7-45.

Austin, N.D., Sahinidis, N.V., Trahan, D.W., 2016-a. Computer-aided molecular design: an introduction and review of tools, applications, and solution techniques. Chem. Eng. Res. Des. 116, 2–26.

Austin, D., Sahinidis, N.V., Trahan, D.W., 2016-b. A COSMO-based approach to computer-aided mixture design. Chem. Eng. Sci. https://doi.org/10.1016/j.ces.2016.05.025.

Begum, S., Raju Achary, P.G., 2018. Optimal descriptor based QSPR models for catalytic activity of propylene polymerization. Int. J. Quantit. Structure-Property Relationships (IJQSPR) 3 (2). https://doi.org/10.4018/IJQSPR.2018070103.

Bekker, C., 2018. Sustainable Use of Medication, Medication Waste and Feasibility of Redispensing Thesis. University of Utrecht Repository, ISBN 978-90-393-7045-2.

Bijl, D., 2019. Rational pharmacotherapy, de-prescribing and green pharmacy. Sustain Chem Pharm 12, 100127.

Bilonda, M.K., Mammino, L., 2017. Intramolecular hydrogen bonds in conformers of quinine and quinidine. An HF, MP2 and DFT study. Molecules 22, 245.

Bushelyev, S.N., Stepanov, N.F., 1989. Elektronnaya Struktura Y Biologhicheskaya Aktivnost Molecul. Khimiya, Snanye, Moscow.

Calisto, V., Esteves, V.I., 2009. Psychiatric pharmaceuticals in the environment. Chemosphere. https://doi.org/10.1016/j.chemosphere.2009.09.021.

Canales, C., Egan, L., Zimmer, M., 1992. Molecular modelling as an inorganic chemistry exercise. J. Chem. Educ. 69 (1), 21–22.

Chtita, S., Bouachrine, M.T., Lakhlifi, T., 2016. Basic approaches and applications of QSAR/QSPR methods. Revue Interdisciplinaire 1, 1.

Casanova, J., 1993. Computer based molecular modelling in the curriculum. J. Chem. Educ. 70 (11), 904–909.

Delaware, D.L., Fountain, K.R., 1996. Computational chemistry in the first organic chemistry course. Applications in an Active Learning situation. J. Chem. Educ. 73 (2), 116–119.

Emara Y., Siegert M.W., Lehmann A., Finkbeiner M., Life cycle management in the pharmaceutical industry using an applicable and robust LCA-based environmental sustainability assessment approach In: E. Benetto, K. Gericke, M. Guiton (Eds), Designing Sustainable Technologies, Products and Policies. 2018. Springer International Publishing AG, Cham Switzerland, pp. 79-88.

Fayet, G., Rotureau, P., 2016. How to use QSPR-type approaches to predict properties in the context of Green Chemistry. Biofuels, Bioproducts & Biorefining 10 (6), 738–752. Wiley.

Gautam, V., Sahni, Y.P., Kumar Jain, S., Shrivastav, A., 2018. Ecopharmacovigilance: an environment safety issue. The Pharma Innovation Journal 7 (5), 234–239.

Gawande, M.B., Bonifácio, V.D.B., Luque, R., Branco, P.S., Varma, R.S., 2013. Benign by design: catalyst-free in-water, on-water green chemical methodologies in organic synthesis. Chem. Soc. Rev. 42, 5522–5551.

Gillom, R.D., 1989. Semiempirical and ab initio calculations of charged species used in the physical organic chemistry course. J. Chem. Educ. 66 (1), 47–50.

Girod, M.. Mark Girod's professional library and resources. www.wou.edu/∼girodm/library/ch9.pdf.

Goerigk, L., Mehta, N., 2019. A trip to the density functional theory zoo: warnings and recommendations for the user. Aust. J. Chem. https://doi.org/10.1071/CH19023.

Goldstein, M., Shenker, M., Chefetz, B., 2014. Insights into the uptake processes of wastewater-borne pharmaceuticals by vegetables. Environ. Sci. Technol. https://doi.org/10.1021/es5008615.

Green, Sustainable Pharmacy. Pharma mirror. Published on November 9, 2013 in Dictionary Online. https://www.pharmamirror.com.

Gruenberg, K., Apollonio, D., MacDougall, C., Brock, T., 2017. Sustainable pharmacy: piloting a session on pharmaceuticals, climate change, and sustainability within a U. S. Pharmacy curriculum. Inov Pharm 8 (4). Article 3. http://pubs.lib.umn.edu/innovations/vol8/.

Gualtero, S., 2005. Pollution prevention measures for unwanted pharmaceuticals. Industrial Ecology. December.

Guérineau, V., Rollet, M., Viel, S., Lepoittevin, B., Costa, L., Saint-Aguet, P., Laurent, R., Roger, P., Gigmes, D., Martini, C., Huc, V., 2019. The synthesis and characterization of giant Calixarenes. Nat. Com. 10, 113. https://doi.org/10.1038/s41467-018-07751-4.

Inayat, A., van Assche, A., Clark, J.H., Farmer, T.J., 2018. Greening the esterification between isosorbide and acetic acid. Sustain Chem Pharm 7, 41–49.

Kaushik, G., Thomas, M.A., 2019. The potential association of psychoactive pharmaceuticals in the environment with human neurological disorders. Sustain Chem Pharm 13, 100148.

Kolpin, D., Furlong, E., Meyer, M., Thurman, E., Zaugg, S., Barber, L., Buxton, H., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1990-2000: a national reconnaissance. Environ. Sci. Technol. 36 (6), 1202–1211.

Kralisch, D., Ott, D., Gericke, D., 2015. Rules and benefits of Life Cycle Assessment in green chemical process and synthesis design: a tutorial review. Green Chem. 17, 123–145.

Kümmerer, K., 2007. Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry. Green Chem. 9, 899–907.

Kümmerer, K., 2019. From a problem to a business opportunity-design of pharmaceuticals for environmental biodegradability. Sustain Chem Pharm 12, 100136.

Levin, R., 1947. Frontiers in group dynamics. II. Channels of group life: social planning and action research. Hum. Relat. 1, 143–159.

López-Serna, R., Jurado, A., Vázquez-Suñé, E., Carrera, J., Petrović, M., Barceló, D., 2013. Occurrence of 95 pharmaceuticals and transformation products in urban groundwaters underlying the metropolis of Barcelona, Spain. Environ. Pollut. 174, 305–315.

Lundell, J., Aksela, M., 2003. Molekyylimallinnus kemian opetuksessa, osa 1: molekyylimallinnus ja kemian opetus, (Molecular modelling and chemistry teaching). Dimensio 67 (5), 47–49.

Mammino, L., 2001. Algunas reflexiones sobre la imagen de la química. Anales de la Real Sociedad Española de Química 97 (2), 48–52.

Mammino, L., Kabanda, M.M., 2008. A computational study of the interactions of the caespitate molecule with water. Int. J. Quant. Chem. 108, 1772–1791.

Mammino, L., Kabanda, M.M., 2012. The geometric isomers of caespitate: a computational study in vacuo and in solution. Int. J. Biol. Biomed. Engin. 6 (1), 14–33.

Mammino, L., Kabanda, M.M., 2014. Considering the medium when studying biologically active molecules: motivation, options and challenges. In: Zaheer-ul-Haq, Madura, J.D. (Eds.), Frontiers in Computational Chemistry. Bentham Science Publishers, pp. 197–256.

Mammino, L., 2015. A great challenge of green chemistry education: the interface between provision of information and behaviour patterns. In: Gomes Zuin, V., Mammino, L. (Eds.), Worldwide Trends in Green Chemistry Education, 1−15. Royal Society of Chemistry.

Mammino, L., 2016. Being consistent with reality: a great challenge for chemistry laboratory reports. In: Kriek, Bantwini, B., Ochonogor, C., Dhlamini, J.J., Goosen, L. (Eds.), ISTE Conference on Mathematics, Science and Technology Education Proceedings. UNISA Press, Pretoria, pp. 428–437.

Mammino, L., 2017. Bowl-shaped structures from acylphloroglucinols: an ab initio and DFT study. Molec. Phys. 115 (17–18), 2254–2266.

Mammino, L., 2018. Incorporating information on green chemistry into theoretical chemistry courses. Current Opinion in Green and Sustainable Chemistry 13, 76–80.

Mammino, L., 2019. Roles of system thinking within green chemistry education. Reflections from identified challenges in a disadvantaged context. J. Chem. Educ. https://doi.org/10.1021/acs.jchemed.9b00302.

Mammino, L., 2020. Five- and six-member bowl-shaped structures from acylphloroglucinols: an ab initio and DFT study. J. Mol. Model. 26 (13) https://doi.org/10.1007/s00894-019-4208-z.

Mathegka, A.D.M., Meyer, J.J.M., Horn, M.M., Drewes, S.E., 2000. An acylated phloroglucinol with antimicrobial properties from *Helichrysum caespititium*. Phytochemistry 53, 93–96.

Meurig Thomas, J., Raja, R., Sankar, G., Bell, R.G., Lewis, D.W., 2001. Benign by design. New catalysts for an environmentally conscious age. Pure Appl. Chem. 73, 1087–1101.

Miller Daniel, P., Adam, Phillips, Herbert, Ludowieg, Sarah, Swihart, Jochen, Autschbach, Eva, Zurek, 2019. The computational design of two-dimensional materials. J Chem. Educ. 96 (10), 2308–2314.
Ochterski Joseph, W., 2014. Using computational chemistry activities to promote learning and retention in a secondary school general chemistry setting. J Chem. Educ. 91 (6), 817–822.
Pandey, P., Dahiya, M., 2016. Int. J. Pharm. Sci. Res. 1 (4), 15–21.
Papa, E., Gramatica, P., 2010. QSPR as a support for the EU REACH regulation and rational design of environmentally safer chemicals: PBT identification from molecular structure. Green Chem. 12, 836–843.
Patti, A.F., Scott, J.L., 12-14 September 2001. Impressions young people have of chemistry – a role for green chemistry?. In: IUPAC Workshop on Green Chemistry Education, Venice. Collection of abstracts, p. 30.
Raimondo, S., Barron, M.G., 2020. Application of Interspecies Correlation Estimation (ICE) models and QSAR in estimating species sensitivity to pesticides. SAR QSAR Environ. Res. 31 (1), 1–18.
Riemenschneider, C., Seiwert, B., Goldstein, M., Al-Raggad, M., Salameh, E., Chefetz, B., Reemtsma, T., 2017. An LC-MS/MS method for the determination of 28 polar environmental contaminants and metabolites in vegetables irrigated with treated municipal wastewater. Anal. Methods 9, 1273–1281.
Sandegren, L., 2019. Low sub-minimal inhibitory concentrations of antibiotics generate new types of resistance. Sustain Chem Pharm 11, 46–4.
Spielmeyer, A., 2018. Occurrence and fate of antibiotics in manure during manure treatments: a short review. Sustain Chem Pharm 9, 76–86.
Summerton, L., Taylor, R.J., Clark, J.H., 2016. Promoting the uptake of green and sustainable methodologies in pharmaceutical synthesis: CHEM21 education and training initiatives. Sustain Chem Pharm 4, 67–76.
Thomas, M.A., Klaper, R.D., 2012. Psychoactive pharmaceuticals induce fish gene expression profiles associated with human idiopathic autism. PloS One. https://doi.org/10.1371/journal.pone.0032917.
Thompson Scott, E., Sears Duane, W., 2005. Simplifying structure analysis projects with customizable chime-based templates. Biochem. Mol. Biol. Educ. 33 (5), 344–350.
Toma, A., Crisan, O., 2018. Green pharmacy – a narrative review. Clujul Med. 91 (No. 4), 391–398.
Tundo, P., Anastas, P., 2000. Green Chemistry, Challenging Perspectives. Oxford University Press, Oxford.
Tundo, P., Patti, T. (Eds.), 2001. IUPAC Workshop on Green Chemistry Education Report. IUPAC & INCA, Venice.
Verma, J., Khedkar, V.M., Coutinho, E.C., 2010. 3D-QSAR in drug design - a review. Curr. Top. Med. Chem. 10, 95–115.
Villaverde, J.J., Sevilla-Morán, B., López-Goti, C., Alonso-Prados, J.L., Sandín-España, P., 2020. QSAR/QSPR models based on quantum chemistry for risk assessment of pesticides according to current European legislation. SAR QSAR Environ. Res. 31 (1), 49–72.