Multi-Objective Modeling of Herbicidal Activity from an Environmentally Friendly Perspective

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ABSTRACT

Despite the attractiveness in weed management, herbicides can produce several hazardous effects due to their persistence in the environment. It is therefore important to strike a balance between the herbicidal activity and ecotoxicological profile. The aim of the present paper is to perform a multi-objective QSPR modeling of the bioactivity and soil sorption profile of a dataset of triazine derivatives, in order to gain understanding on the structural features favoring both high herbicidal activity and low soil sorption. To this end, the Photosynthetic Electron Transport (PET) inhibitory activity and the logKOC are selected, and a MIA-QSPR model is built for the pI50/log Koc ratio. The obtained model presented satisfactory performance evidenced by the calibration and validation parameters. Structural interpretation of the built model is performed using the recently implemented MIA-Plot tool, providing important guidelines on the structural moieties related with high pI50/logKOC ratio values as a desirable requirement in the development of high activity and eco-friendly triazines.

KEYWORDS

MIA-QSAR, Partial Least Squares, PET Inhibitory Activity, Soil Sorption, Triazines

INTRODUCTION

Agricultural weed management continues to rely heavily on chemical control methods using herbicides (Gianessi, 2013). However, numerous studies have long demonstrated that these chemicals may produce several hazardous effects due to their persistence in the environment, which results in their incorporation in the food chain at different trophic levels, through the processes of bioconcentration and/or soil sorption (Buchanan et al., 2009). Consequently, research efforts have been entrenched in the search of more ecofriendly herbicides with a reduced propensity to bioaccumulate in aquatic organisms or persist in soils or sediments (Freitas, Barigye, Daré, & Freitas, 2016; Saxena & Pandey, 2001; Varejão, Demuner, Barbosa, & Barreto, 2013). On the other hand, weed species have continuously adapted and thus developing resistance to commonly used herbicides and thus increasing the pressure on the chemical industry to develop new chemicals with strong herbicidal activity (Renton, Busi, Neve, Thornby, & Vila-Aiub, 2014).

A deep analysis of the reports in the literature shows that these two objectives have been pursued separately (Bettiol et al., 2016; Clark, 2012; Ghose & Crippen, 1987; Larif et al., 2013; Liu & Qian, 1995; Morita, Nagare, & Hayashi, 1987; Varejão et al., 2014). However, seeking to
reduce the bioconcentration and/or soil sorption tendency of chemicals may result in the loss/lower herbicidal activity and vice-versa as chemical structural properties are not necessarily orthogonal. To contextualize better this point, bioconcentration and soil sorption described by the bioconcentration factor (BCF) and the soil/water–organic carbon partition coefficient (log KOC), respectively, are known to possess a strong relationship with the physicochemical parameter n-octanol/water partition coefficient (log P) and in principle compounds with lower log P values should have a lower tendency to bioconcentrate or to interact strongly with soil particles. However, low logP compounds may just as well be ineffective inhibitors due to failure to penetrate the lipophilic plant tissue. Therefore, the search of a successful herbicide candidate should be as a result of striking a compromise between various objectives, which sometimes may unfortunately compete among each other.

In this sense, the aim of the present paper is to perform a multi-objective modeling experiment of the inhibitory activity and ecotoxicological profile of the triazine derivatives, which is a family of well-known and widely used herbicides, with the goal of understanding the structural features that favor high herbicidal activity and paralleled with a favorable environmental profile. In the modeling of the herbicidal activity, it is important that a plant species independent target is considered, to allow for a broad spectrum analysis. In this sense, the Photosynthetic Electron Transport (PET) inhibitory activity is selected as the property to be maximized while the log KOC is to be minimized.

The Quantitative Structure-Property Relationships (QSPR) studies play an important role in the prediction of molecular properties and consequently in the virtual screening of chemical compound libraries for molecular entities of interest. This methodology is centered on the principle that there exists a close relationship between the structural characteristics of chemical compounds and their chemical, physicochemical and biological properties. Several parameters for characterizing chemical structures, ranging from 0D – 6D approaches have been reported in the literature (Barigye, Marrero-Ponce, Pérez-Giménez, & Bonchev, 2014; Todeschini & Consonni, 2009). While, each of these approaches presents particular advantages and drawbacks, a tradeoff between simplicity and modeling power is largely considered as beneficial. In this sense, the multivariate image analysis applied to quantitative structure-property relationships (MIA-QSPR) method appears to be an interesting approach in molecular modeling (Barigye & Freitas, 2016).

This is a simple alignment-based approach based on the understanding that 2D chemical structure images contain relevant topochemical and topostructural information, useful for modeling chemical, physicochemical and biological properties of molecules (Antunes, Freitas, & Rittner, 2008; Bitencourt & Freitas, 2008; Cormannich, Freitas, & Rittner, 2011; Duarte, Barigye, da Mota, & Freitas, 2015; Duarte, Barigye, & Freitas, 2014; Duarte, Barigye, & Freitas, 2015; Freitas, da Cunha, Ramalho, & Goodarzi, 2008; Goodarzi & Freitas, 2008; Goodarzi, Freitas, & Ramalho, 2009; Guimarães, Mota, Silva, & Freitas, 2014; Silla et al., 2011). Viewed from digital image processing standpoint, an image is basically comprised of an array of pixels arranged to yield different patterns according to a desired chemical image. Consequently, in order to employ these images as molecular descriptors, the numeric values for these pixels are considered.

Originally, the MIA-QSPR approach was based on simple black and white wire-frame chemical structure graphs (Freitas, Brown, & Martins, 2005). Although this scheme yielded good correlations in modeling experiments, the failure to discriminate hetero atoms and/or atom types resulted in redundancy. As a result, color schemes based on the RGB system were incorporated to yield an improved framework in which structural features, such as atom types and size, based on well-known atomic properties (e.g. electronegativity and van der Waals radii) were consequently codified (Barigye & Freitas, 2016; Duarte et al., 2015; Duarte et al., 2015; Guimarães et al., 2014; Nunes & Freitas, 2013). This scheme, codenamed asaug-MIA-QSPR (acronym of augmented Multivariate Image
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