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QSPR Models of β-dihydroagarofuran Derivatives:
Exploring Lead Compounds for Pesticides

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ABSTRACT

The use of chemical pesticides, although the most effective method for controlling insects, may in the long-term result in pest resistance development as well as it may impact on food quality, the environment and human health. Therefore, the botanical insecticides are interesting alternatives to minimize these undesirable effects, including a secondary metabolite in the Celastraceae family. Thus, a QSPR study was conducted for β-dihidroagarofuran derivatives with pesticide properties in order to identify features that may improve the potency thereof. The best model obtained from alignment 3 showed values of Q^2=0.657, R^2=0.757, R^2p=0672 and $R^2m(test)$=0.509, indicating good predictive ability and statistical robustness. Moreover, the descriptors presented important pharmacophore groups for the development of new pesticides.

KEYWORDS

β-dihidroagarofuran, Mortality, Natural Pesticides, QSPR

INTRODUCTION

Currently, the increasing use of large amounts of pesticides and fertilizers in plantations has become essential to maximize agricultural productivity, as the human population is constantly growing, thus sustainable food production is a major challenge faced by the agricultural sector worldwide (de Oliveira, 2014).

Chemical pesticides are still the most effective method for pest control in agriculture however their use in the long-term results in the development of resistance by the insects and impacts food quality, producing serious threats to human health and the environment, which requires the conception of pesticides with new modes of action (de Oliveira, 2014; Zhao, 2016). Therefore, it is necessary to find less aggressive compounds as an alternative to be used as pesticides. Considering this, the botanical pesticides and/or compounds based on natural products have been identified as interesting alternatives to synthetic chemical pesticides in controlling pests, because apparently, they pose little threat to human health and the environment (Isman, 2006, pp. 45-66).

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Plants from the Celastraceae family have a secondary metabolite in the class of sesquiterpenes with β-dihidroagarofuran skeleton which have broad biological activity as immunosuppressant (Duan et al., 2001), cytotoxic (Kuo et al., 1994), anti-HIV (Gonzàlez et al., 1989) and antitumor (Ujita, 1993; Takaishi, 1992). On top of that, they also have insecticidal activity (Mingan, 2006; Zhiqing, 2007; Wei, 2009, Zhao, 2016), and some of its derivatives have been used in plantations in China (Wei et al., 2009).

In order to identify important structural characteristics for the action of these compounds, studies of quantitative structure-property relation (QSPR) are of great value, since this methodology allows the theoretical analysis of a great number of compounds, providing the means to reduce time and cost for the development of new structures (Gajo, 2016; Senese, 2004). Methods of QSPR, and other related approaches are based on the principle that within a class of compounds small structural changes may cause changes in their properties, therefore, mathematical relationships are established, which correlate a set of molecular descriptors and the biological response of interest. Among the QSPR methodologies, the analysis in four dimensions stands out, as it incorporates the conformational freedom in the development of mathematical models. The 4D formalism was developed to handle the main problems inherent the to the 3D analysis, namely the identification of representative conformation and definition of the molecular alignment. Furthermore, from the analysis of molecular descriptors it is possible to relate how individual regions of the compounds contribute to their biological effect (Hopfinger et al., 1997). This methodology has not been explored in depth, in pesticide development, but their use in medicinal chemistry for the prediction of new compounds activity has been greatly employed in the literature (Sodero, 2012; Martins, 2009; Santos-Filho & Hopfinger, 2002; Silva, 2014; Assis, 2016; Gajo, 2016; Santos-Garcia, 2016).

In this sense, the aim of this study is to apply the QSPR methodology in the analysis of β-dihidroagarofuran derivatives in search of structural characteristics that explain their mortality rate.

MATERIALS AND METHODS

Biological Data

Fifty-one compounds derived from β-dihydroagarofuran were used to develop the QSPR models. These compounds were synthesized and evaluated experimentally by Zhao et al (Zhao 2016). Table 1 lists the structures of the compounds with their mortality rates. The mortality rates were evaluated with the Third-Instar Larvae of *M. separata* at a concentration of 40mg/mL within 36 h. For each compound, thirty larvaes were tested. Acetone and celangulin-V served as blank and positive control, respectively. Through *in vivo* tests it is possible to evaluate the metabolism, efficacy and toxic potential of the compounds.

The QSPR models were built using 41 compounds, the training set, and externally validated using 10 compounds, the test set. Three distinct test sets were evaluated, all selected randomly, being chosen 20% of the compounds throughout the entire range of values of mortality in order to obtain reliable models. The test group 1 includes molecules 8, 11, 17, 25, 26, 31, 39, 44, 46 and 50; in the test group 2 are 8, 15, 17, 26, 33, 36, 37, 40, 44 and 47; and in the test 3 molecules 1, 3, 5, 10, 15, 18, 22, 43, 45, 48.

Molecular Dynamics Simulation

The three-dimensional structures of the compounds (Table 1) were modeled by the *HyperChem* software (Laxmi, & Priyadarshy, 2002), the structures were optimized and the partial atomic charges were calculated using the semi-empirical method RM1 (Rocha et al., 2005). The compounds were subject to molecular dynamics simulation process (SDM), in order to generate a conformational ensemble profile (CEP) for each structure, thereby exploring the conformational flexibility of the compounds (4D-QSAR, 1997; Hopfinger, 1997; Gajo, 2016). The simulation time used was 100 ps with 0.001 ps intervals, and the simulation temperature was 300K. To simulate the effect of the solvent, a dielectric constant dependent on the distance was applied (Hopfinger et al., 1997).

Use of Ionic Liquids and DES for Synthesis of Medicinally Important 1,2,3-Triazole Scaffolds