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Modified neonicotinoid insecticide with bi-directional selective toxicity and drug resistance

Yuanyuan Zhao[a,b], Yu Li[a,b,*]

[a] College of Environmental Science and Engineering, North China Electric Power University, Beijing 102206, China
[b] The State Key Laboratory of Regional Optimisation of Energy System, North China Electric Power University, Beijing 102206, China

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ABSTRACT

A three-dimensional quantitative structure–activity relationship (3D-QSAR) model was established based on the molecular structures and the negative logarithm of experimental lethal concentration 50 values (pLC_{50}) of neonicotinoid insecticides. Then, the mechanisms of bi-directional selective toxic effects and drug resistance were determined using homology modeling and molecular docking analyses. The results of the model showed that the 1-, 2-, 4-, and 12- positions of neonicotinoid insecticides strongly affected their toxicity, and that the introduction of bulky or electropositive groups at these positions could increase the pLC_{50} values. Using Compound 19 as a template, we designed 37 derivatives with greater toxicity (increased by 0.04–11.45%). Among them, 20 derivatives had bioconcentrations lower than that of Compound 19 (reduced by 0.38–147.88%). Further screening of Compound 19 and the 20 derivatives mentioned above by homology modeling and acetylcholine receptors (AChRs) molecular docking analyses showed that 10 derivatives had bi-directional selective toxic effects against pests and bees. Further docking analyses of Compound 19 and these 10 derivatives identified that Derivative-33 showed decreased docking with superoxide dismutase (SOD) and glutathione S transferase (GST) in pests and enhanced docking with these enzymes in bees, indicating bi-directional selective resistance for pests and bees. Accordingly, Derivative-33 was selected as a new insecticide with high toxicity to pests and low toxicity to bees (bi-directional selective toxicity), low resistance in pest populations, and high resistance in bee populations. This study provides valuable reference data and will be useful for the development of strategies to produce new environmentally friendly pesticides.

1. Introduction

After pyrethroid insecticides, neonicotinoid insecticides represent a major breakthrough in the history of insecticides (European, 2013). As nicotinic acetylcholine receptor agonists, the mode of action of neonicotinoids is relatively novel (Nagata et al., 1997). The principle is to hinder the conductance of cholinergic signals in insects, which causes the insects to become excessively excited or paralyzed, and then to lose control of their behavior (Johnson, 2015). Neonicotinoid insecticides have selective toxicity and can effectively control pests such as mammals and whitefly. However, despite their selective toxicity, these insecticides have been linked with massive declines in the global population of pollinating insects such as bees (Millar and Denholm, 2007).

In 1999, France prohibited the use of imidacloprid on sunflowers because it was toxic to bees. However, because of outdated or ineffective methods to evaluate the subacute and chronic toxicity of pesticides and their effects on the growth, development, and reproduction of bees, many countries still permit the use of these insecticides (Bonmatin et al., 2005). In 2006, Claudianos et al. (2006) found that, compared with other insects, bees had fewer genes encoding detoxification enzymes in their genomes, making them more vulnerable to pesticides. In the United States, Canada, France, Germany, Sweden, and other countries, many bee colonies decreased or disappeared within a single year in a phenomenon known as colony collapse disorder (CCD). Approximately 65.10–87.50 million bees disappeared in the United States during this period, triggering a crop pollination crisis (Johnson, 2007). To address this situation, a CCD research group was established to filter and detect 117 chemical substances in the sick bee samples. The group identified the neonicotinoid insecticides as the main cause of the crisis (Stokstad, 2007). In 2013, Tapparo et al. (2013) used liquid chromatography-mass spectrometry to analyze neonicotinoid insecticides at ultra-trace levels, and determined that these insecticides, even at nanogram levels, were strongly toxic to bees.

In addition to their effects on bees, neonicotinoid insecticides have

* Corresponding author at: College of Environmental Science and Engineering, North China Electric Power University, Beijing 102206, China.
E-mail addresses: zyy950210@outlook.com (Y. Zhao), liyuxx8@hotmail.com, liyuxx@jlu.edu.cn (Y. Li).

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also resulted in the emergence of drug resistance because of their widespread use to control pests in the fields of health and agriculture (Denholm et al., 2002). This has resulted in resistant insect populations that can tolerate dosages that would kill the majority of individuals in normal populations (Ji, 2017). Because of the selective effect of insecticides used over a long period of time, many insects have developed various degrees of resistance. The development of resistance will have many adverse effects, such as decreased crop yields, higher planting costs, and greater pesticide use (Joußen et al., 2012). Therefore, the prevention and control of resistance and the development of new insecticides are important research goals.

The earliest record of insect resistance was in 1908, when Melander et al. Anonymous (2011) found a population of *Quadraspidiotus perniciosus* (Comstock) in a Californian pear orchard that was resistant to lime sulfur. Soon afterwards, *Aonidiella aurantii* (Maskell) resistant to hydrocyanic acid and codling moth resistant to lead arsenate were discovered. By 2011, at least 600 kinds of insects and mites were known to be resistant to one or more pesticides, with the Diptera and Lepidoptera having the largest numbers of resistant members (Bruck et al., 2011). One year later, the number of resistant insect species had increased to more than 1000 (Riveron et al., 2013). Many studies have suggested that the mechanism of drug resistance is the enhanced activity of detoxification enzyme(s) in insects, which results in decreased metabolic resistance and target sensitivity (Assogba et al., 2014; Sven et al., 2010; Zhang et al., 2008).

The aim of this study was to explore the mechanism of toxicity of neonicotinoid insecticides towards bees and pests, and to evaluate the effects of various neonicotinoid insecticides to induce resistance in insects. Accordingly, Derivative-33 were screened by three-dimensional quantitative structure–activity relationship (3D-QSAR) model, homology modeling and molecular docking analyses, which has higher toxicity, lower bioconcentration effects, bi-directional selective toxicity and resistance-inducing (Chen et al., 2016). This theoretical method could be used to produce new environmentally friendly neonicotinoid insecticides with bi-directional selective toxicity and resistance-inducing effects on pests and bees.

2. Materials and methods

2.1. Data

The 3D-QSAR model was analyzed with SYBYL software (Tripos Assoc., St Louis, MO, USA) (Gu et al., 2016). The experimental data for neonicotinoid insecticides were obtained from Li et al. Tian et al. (2007a, 2007b); Shao et al. (2009, 2010); Tian et al. (2007c). We used the negative logarithm of experimental lethal concentration 50 values (pLC_{50}) as the experimental data, and selected 23 compounds as a training set and 8 compounds as a test set to establish the 3D-QSAR model. The 30 compounds were selected to represent diverse structures and universal distribution (Aouidate et al., 2017).

2.2. 3D-QSAR model for toxicity of neonicotinoid insecticides

2.2.1. Molecular structure optimization and alignment of neonicotinoid insecticides

The molecular structures were drawn using SYBYL software and then optimized to obtain the most stable conformations. To optimize compounds, we used the Tripos Force Field and Minimize programs with Gasteiger-Hückel charges, and Powell's method (maximum number of optimizations, 10,000; energy convergence gradient value, 0.005 kJ/mol, and all other parameters set to default values) (Gu et al., 2017). All of the compounds had characteristic elements in the labeled region as the common framework. We used Compound 19, which had the highest pLC_{50} value (8.74), as the target to align the other molecules (Fig. 1). All of the compounds could be well aligned.

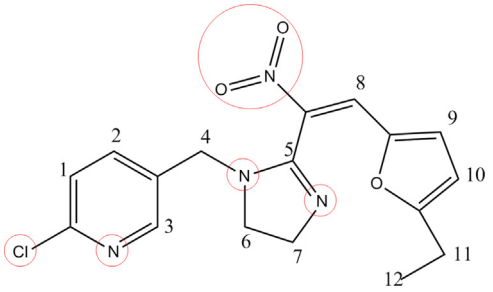

Fig. 1. Selection of target compound to align common framework.

2.2.2. Modeling of neonicotinoid insecticides with CoMFA and CoMSIA

In the QSAR module, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) analysis methods could be chosen. The electrostatic field and steric field were calculated using the CoMFA method. The dielectric constant was related to distance (threshold, 125.4 kJ/mol; other parameters set to default values). The pLC_{50} values of 30 neonicotinoid insecticides were entered into the training table, and the parameters of the model were calculated automatically by Autofill using SYBYL. A partial least-squares regression analysis was applied to establish the relationships between the structure and the biological activity of the target compound. First, we used the leave-one-out method to cross-validate the compounds in the training set, and determined (Li et al., 2013).

Compared with the CoMFA model, the CoMSIA model increased the hydrophobic field and the hydrogen-bond donor and acceptor fields using Gaussian similarity functions. The results of the CoMSIA method were almost unaffected by the rules of compound matching, and the CoMSIA method explained the structure–activity relationship of a compound more intuitively than did the CoMFA method. Although the CoMSIA method does not have some of the drawbacks of the CoMFA method, it does not necessarily provide better results (Wang et al., 2017a). Therefore, to obtain a reliable prediction model, we used the two methods to validate and complement each other.

2.2.3. Modification of neonicotinoid insecticides based on contour maps

In the CoMFA and CoMSIA models, Compound 19 had the highest pLC_{50} value (8.74), which showed that it had the strongest toxicity effect. Therefore, we chose to modify Compound 19 to ensure that the toxicity effects of the congeners were increased significantly. In the contour maps, differently colored contours showed the influence of the different fields on the pLC_{50} values of the neonicotinoid insecticides. In the steric field, green contours showed that bulky groups increased the activities of the molecules, while yellow contours showed that bulky groups decreased the activities of the molecules. In the electrostatic field, blue contours showed that positive charges increased the activities of the molecules, and red contours showed that negative charges decreased the activities of the molecules. In the hydrophobic field, white contours showed that hydrophilic charges increased the activities of the molecules, and yellow contours showed that hydrophobic charges decreased the activities of the molecules. In the hydrogen bond donor field, blue contours showed that a hydrogen bond donor increased the activities of the molecules, and purple contours showed that a hydrogen bond donor decreased the activities of the molecules. In the hydrogen bond acceptor field, purple contours showed that a hydrogen bond acceptor increased the activities of the molecules, and red contours showed that a hydrogen bond acceptor decreased the activities of the molecules (Tong et al., 2017; Wang et al., 2017b).

2.3. Homology modeling for acetylcholine receptors (AChRs), superoxide dismutase (SOD), and glutathione S transferase (GST) docking ability

The homology modeling algorithm is a recognized method to predict the structure of a protein from its amino acid sequence. The amino