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Review

Turning renewable resources into value-added products: Development of rosin-based insecticide candidates

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A B S T R A C T

Rosin is extensively distributed and renewable natural resource in China. In continuation of our research on natural product-based insecticidal agents endowed with eco-friendly properties, 37 rosin-based amide derivatives containing thiadiazole group were prepared. Meanwhile, the structures of rosin-based derivatives containing thiadiazole group were characterized by melting point, IR spectroscopy, ^{1}H NMR, elemental analysis, ESI-MS and X-ray crystallography. In addition, the insecticidal activities of rosin-based amide derivatives containing thiadiazole group (3a–w and 7a–n) against *Mythimna separata* and *Plutella xylostella* were investigated. Compounds 3p–r, 7f and 7n (with LC_{50} values of 0.222, 0.222, 0.224, 0.223 and 0.214 μg/mL) displayed outstanding insecticidal activity in comparison with flunbendiamide (a commercial insecticide, with LC_{50} value of 0.222 μg/mL). The optimal conformers and best multilinear regression analysis were performed by Gaussian and CODESSA software package, and five descriptors correlating the molecular structures with their insecticidal activities were selected as follows: HOMO–LUMO, log MV, log P, Total Charge I and Total Charge II. For this built QSAR model, the correlation coefficient (R^2) was 0.9604, the squared standard error of the estimates (S^2) was 0.0052, and the Fisher significance ratio (F) was 103.79. The preliminary SAR and QSAR studies showed that electronic and steric effect of target compounds had an important influence on the larvicidal activity.

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1. Introduction

Severe environmental concerns and drug resistance to insects have occurred due to long-term and excess usage of traditional agrochemicals for many years (Lahm et al., 2007). As a feasible solution, the discovery of new insecticides from renewable natural products or natural product-based derivatives is an essential component in integrated pest and disease management of modern agricultural industry (Cantrell et al., 2012).

Rosin is widely distributed terpenoid renewable resource in the world (Li et al., 2012a). Recently, rosin has been used as start active materials due to its broad range of bioactivities, such as plant growth regulation, anticancer, antibacterial, anti inflammation, etc (Alvarez-Manzaneda et al., 2006). The series of diamides insecticides with acrylpimaric acid (APA) backbone structure were reported in our previous work. It was disappointed that these rosin derivatives displayed lower insecticidal activity against oriental armworm (*Mythimna separata*) and mild larvicidal activity against diamondback moth (*Plutella xylostella*). Interestingly, parts of thiadiazole-containing diamides displayed significant larvicidal activity against *P. xylostella* (Li et al., 2014a). Additionally, structure and/or quantitative structure activity relationship (SAR and/or QSAR) studies indicated that steric effect of title compounds played a vital role on the larvicidal activity. As part of a broader effort to improve the physical properties of these rosin-based derivatives in order to optimize their biological activity, the steric effect of rosin-based amide compounds was reduced by replacing rosin–acrylic acid adduct (RAAA) backbone structure with dehydroabietic acid (DHA) backbone structure as shown in Fig. 1. Meanwhile, thiadiazole heterocyclic group has been documented to show a wide range of bioactivities, for instance, insecticidal, antimicrobic, antifungal, antineoplastic, herbicidal, etc (Gomha et al., 2015; Lin et al., 2014; Popiołek et al., 2015; Sobhy et al., 2012; Suzuki et al., 2011; Wang et al., 2011). Enlightened by all of the descriptions above, 37 rosin-based amide derivatives containing thiadiazole group were synthesized. Among them, 23 DHA amide derivatives containing thiadiazole group were new compounds.

It is virtually and economically impossible in developing and screening candidates with insecticidal activity from numberless compounds (Naik et al., 2009; Xu et al., 2009). The application of QSAR study is one shortcut to resolve the cost and time issues (Hansch and Verma, 2009). On the basis of analysis results of QSAR, many important physiochemical properties correlating with the insecticidal activity can be determined, which may enlighten with the design and development of potential rosin-based pesticides (Liu et al., 2010; Speck-Planche et al., 2012). However, there are few reports on the further research on QSAR of laricidal agents from rosin.

Hence, in this study, 37 rosin-based amide derivatives containing thiadiazole group were prepared. Meanwhile, the insecticidal activities of rosin-based amide derivatives containing thiadiazole group (3a–w and 7a–n) against *M. separate* and *P. xylostella* were investigated. The QSAR model of rosin-based amide derivatives correlating with their insecticidal activity was built by software packages of Gaussian and CODESSA in this work. Some critical structure factors of affecting the insecticidal activity can be understood thoroughly through interpretation the physical and chemical significance of the chosen descriptors.

2. Materials and methods

2.1. Syntheses and characterizations

The FT-IR spectra of dried compounds were measured by the Nicolet IS10 Fourier transform infrared spectrophotometer (Thermo Nicolet Co., Madison, USA), using a KBr pellets technique. The proton nuclear magnetic resonance (^{1}H NMR) spectra were measured by the Bruker AV-300 (300 MHz) spectrometer and ESI mass spectral data were obtained by a Bruker Q-TOF mass spectrometer (Bruker Co., Karlsruhe, Germany) using tetramethylsilane as an internal reference and $CDCl_3$ or DMSO-d_6 as the solvent. Melting points were measured using a XT-5 microscope melting point measuring apparatus (Saiao Co., Beijing, China) and without correcting thermometer. Thin-layer chromatography (TLC) analysis was used to monitor reactions, which was performed using Merck silica gel 60 GF254 plates, visualized under 254 nm UV light and eluted with ethyl acetate/etroleum ether (1:5, v:v). The elemental analysis was performed on Vario EL-III (Elementar Co., Hanau, Germany). X-ray intensity data were recorded by a Bruker/Enraf-Nonius CAD-4 diffractometer at 293K. All reagents were chemically pure (CP), besides rosin and DHA were crude product purchased from Wuzhou Pine Chemicals Ltd. and used directly without treatment.

2.1.1. Synthesis of 5-dehydroabietyl-2-azyl-1,3,4-thiadiazole (2)

Thiosemicarbazide (0.95 g; 0.01 mol) and 1 (DHA, 3.00 g; 0.01 mol) were mixed in phosphorus oxychloride ($POCl_3$, 25 mL). After refluxing for 4 h, the hydrogen ion concentration value of reactant was regulated to ten and a yellow solid precipitated out. The crude product was obtained by filtration and vacuum drying. Recrystallization from ethanol gave the compound 2.

2.1.2. Synthesis of N-[5-dehydroabietyl-[1,3,4]thiadiazol-2-yl]-amide (3a–w)

15 mL of dichloromethane with dissolved alkyl or aryl chloride (0.01 mol) was dropped to 40 mL of dichloromethane solution of (2) (3.55 g; 0.01 mol) and 0.03 mol Et_3N at low temperature (<5 °C).