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Additive effects on the improvement of insecticidal activity: Design, synthesis, and insecticidal activity of novel pymetrozine derivatives

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ABSTRACT

A series of new pymetrozine analogues containing both methyl on the imine carbon and phenoxy group at the pyridine ring were designed and synthesized. Their insecticidal activities against bean aphid (*Aphis craccivora*), mosquito larvae (*Culex pipiens pallens*), cotton bollworm (*Helicoverpa armigera*), corn borer (*Ostrinia nubilalis*) and oriental armyworm (*Mythimna separata*) were evaluated. The results of bioassays indicated that most of the target compounds showed good insecticidal activity against bean aphid; especially, **IIIf** (80%) and **IIIl** (80%) exhibited higher aphicidal activity than pymetrozine (30%) at 5 mg/kg, and the two compounds still showed 20% and 30% mortality at 2.5 mg/kg, respectively, whereas pymetrozine displayed no activity at the same concentration. These compounds exhibited a completely different structure–activity relationship to that of known pymetrozine derivatives, in which it is thought introducing alkyl group on the imine carbon could be detrimental to the activities. Our new result suggested that the methyl on the imine carbon and phenoxy group at the pyridine ring of phenoxy group may play additive effects on the improvement of aphicidal activity. Besides this, compound **IIIs**, containing an allyl at the *para* position of phenoxy group, exhibited excellent insecticidal activity against mosquito larvae, lepidoptera pests cotton bollworm, corn borer and oriental armyworm.

1. Introduction

Aphids, which have an extremely short life cycle, a high reproductive rate and an efficient dispersal strategy,[1] cause considerable damage to agriculture or horticulture either by feeding on the vascular system or transmission of plant viruses.[2] But to now, only a few natural enemies, such as parasitoids and predators, can reduce the aphid populations under field conditions.[3] There are also some synthetic aphicides, but many of them belong to carbamates, organophosphorus compounds, neonicotinoids, which hold a considerable risk of becoming ineffective due to the build-up of resistance.[4] To overcome this problem, there is an imperative need to research and develop aphicides with new mode of action.

Pymetrozine (Fig. 1), a pyridine azomethine compound discovered by Ciba-Geigy Corp (now Syngenta International AG) in 1989, represents a novel insecticide with a selective activity against aphids, whiteflies, and planthoppers.[5] It is a neuroactive insecticide affecting the nerve that controls the salivary pump of some sucking pests, causing irreversible cessation of feeding, followed by starvation and death. In the IRAC classification, it is classified as 9B (modulators of chordotonal organs) which is very close to flonicamid (classified as 9C).[6] This meant they had novel modes of action compared to other groups of insecticides and showed no cross-resistance with them.[7] Pymetrozine derivatives have attracted considerable attention for decades. Recently, the mode of action of the insecticides pymetrozine and pyrifluquinanzon were published. The two insecticides act selectively on a novel transient receptor potential (TRP) ion channel complex as the target protein. By activating this TRP ion channel complex, the insecticides overstimulate the stretch receptors, disturbing insect locomotion and feeding.[8] However, the structure of TRP ion channel complex is unknown. Thus, the modification of pymetrozine relies more on the analysis of known structure–activity relationships of pymetrozine derivatives. Previous research showed that the insecticidal activity was significantly decreased when the hydrogen atom of the imino group (CH=N) in pymetrozine was replaced by an alkyl group (compound **I**).[9] Therefore, most of the work thereafter focused on the modifications of triazine ring,[10–13] pyridine ring[14–18] and not the linkage part between them.

A substituted phenoxy group is a multifunctional substituent that can adjust the polarity, electronic effect, and steric effect of the molecules, so it is widely used in the field of pesticide and drug

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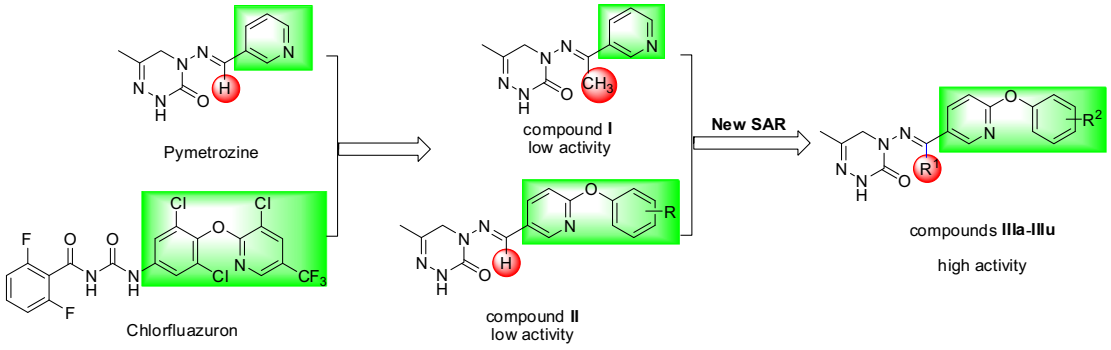

Figure 1. Design of target compounds.

molecular design. For example, chlorfluazuron discovered by Ishihara Sangyo Kaisha Ltd as an insect growth regulator contains a phenoxy group.[19] In our research we planed to introduce phenoxy group onto pymetrozine in order to increase its activity. However, when we introduced phenoxy group to the 4,5-dihydro-1,2,4-triazin-3(2*H*)-one derivatives (compound **II**), **II** did not exhibit good insecticidal activity against aphids. But pleasantly surprised, the aphicidal activity was significantly increased when the hydrogen atom on the imino group (CH═N) of compound **II** was replaced by a methyl group (compound **IIIa**) at the same time. This is a new structure–activity relationship which is different to that of pymetrozine derivatives. In the previous study it was thought that the introduction of alkyl to the imino group was detrimental to the biological activities.[9] We think it is probably the synergistic effect of the methyl and phenoxy group that increases the insecticidal activity. In order to investigate what combination could give better results, a series of pymetrozine analogues containing different substituents (R^1) at the linkage part and different substituents (R^2) on the phenoxy ring attached to the pyridine ring (compounds **IIIa**–**IIIu**) were designed and synthesized. The aphicidal activities of the target compounds against bean aphid (*Aphis craccivora*), as well as insecticidal activities against cotton bollworm (*Helicoverpa armigera*), corn borer (*Ostrinia nubilalis*), oriental armyworm (*Mythimna separata*) and mosquito (*Culex pipiens pallens*), were tested and discussed.

2. Results and discussion

2.1. Chemistry

The synthetic routes of the target compounds **I**, **II**, **IIIa**–**IIIu** are shown in Scheme 1. The key intermediate 4-amino-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**1**) was prepared according to the method in the literature.[18] Compound **1** was condensed with 1-(pyridin-3-yl)ethanone (**2**) to give the imine compound **I** using *p*-toluene sulfonic acid as catalyst. The intermediate aldehyde **4** was synthesized from 6-chloronicotinaldehyde (**3**) and phenol through Williamson ether synthesis in DMF, Cs_2CO_3 as a base, and CuCl as a catalyst.[20,21] Compound **1** reacted with aldehyde **4** giving compound **II**.

The compounds **6a**–**6d** were obtained by reacting phenol with various pyridyl ketones (**5a**–**5d**). In the initial process of preparing compound **6a**, when 1-(6-chloropyridin-3-yl)ethanone (**5a**) (1 equiv) was mixed with phenol (1 equiv) in DMF in the presence of Cs_2CO_3 and CuCl, we found that the reaction didn't occur even after the mixture was refluxed for 12 h. We assumed that the basicity of Cs_2CO_3 was insufficient for the reaction. Hence, we chose NaH as alkali and dimethylsulfoxide as solvent, and then the reaction was complete in 12 h and successfully afforded **6a**. Compounds **6b**–**6d** were synthesized using the same procedure as for **6a**. Similarly as described above, **6a**–**6u** were transformed to corresponding **IIIa**–**IIIu** by reacting with compound **1**.

The title compounds have all been characterized by melting point, ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry (HRMS). All spectral data were consistent with the assigned structures. Since the NMR data indicated all compounds existed in single configuration, we assumed that the 1,2,4-triazin-3(2*H*)-one ring and phenoxypyridine ring have trans configuration.

2.2. Biological evaluation

2.2.1. Foliar contact activity against bean aphid (*A. craccivora*)

The foliar contact activity against bean aphid of the synthesized compounds **I**, **II**, **IIIa**–**IIIu** are shown in Table 1 in comparison to pymetrozine. Compound **II**, with a phenoxy ring attached to the pyridine ring, exhibited much lower activity than pymetrozine; compound **I**, with a methyl at the imino group (CH═N), also exhibited much lower activity, which was consistent with the previously reported data.[9] But to our surprise, compared with **I** and **II**, the aphicidal activity of **IIIa** which is bearing a methyl on the imino group and a phenoxy group at the pyridine ring was significantly increased. Changing methyl to ethyl (**IIIb**), isopropyl (**IIIc**) or trifluoromethyl (**IIId**), the activity was slightly decreased in comparison with **IIIa**. Then, keeping the methyl at the imine group, different substituted-phenoxy group were introduced to the pyridine ring. Most of the compounds showed 100% activity at 100 mg/kg. Especially, **IIIf** (80%) and **IIIl** (80%) exhibited higher activities than pymetrozine (30%) at 5 mg/kg, and they still showed 20% and 30% mortality at 2.5 mg/kg, respectively, whereas pymetrozine showed no activity at the lower concentration. The result indicated that the additive effect of the methyl and phenoxy group play an important role in the aphicidal activity. In addition, the properties and positions of these substituents on the phenoxy ring have an important influence on the activities of these compounds. Compound **IIIl** (30% at 2.5 mg/kg), having a *tert*-butyl at the *para* position of benzene ring, exhibited much higher activity than compound **IIIg** (30% at 10 mg/kg), which has a *tert*-butyl at the *ortho* position of benzene ring.

2.2.2. Toxicity against mosquito larvae

The larvacidal activity against mosquito of the synthesized compounds **I**, **II**, **IIIa**–**IIIu** are shown in Tables 2 and 4 in comparison to pymetrozine. Most compounds exhibited excellent larvicidal activities against mosquito. In particular, the activities of compounds **IIIg**, **IIIl**, **IIIp**, **IIIq** and **IIIs** were much higher than the activity of pymetrozine, and compound **IIIs** exhibited the best larvicidal activity, which had 20% mortality even at 0.01 mg/kg. The position of the substituent on the benzene ring of the target