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Synthesis and insecticidal evaluation of tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one derivatives

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ABSTRACT

A series of novel tetrahydroimidazo[1,2-*a*]pyridine-5(1*H*)-one derivatives containing a electronegative pharmacophore (=CNO_2) were synthesized *via* practical aza-ene reaction and characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. Preliminary bioassays showed that some of the target compounds exhibited good insecticidal activity against brown planthopper (*Nilaparvata lugens*) and cowpea aphids (*Aphis craccivora*) at 500 mg L^{-1}. Among them, compound **11h** was active against brown planthopper at 100 mg L^{-1}. The insecticidal activities varied significantly depending on the types and patterns of the substituents, which provided guidance for further investigation on structure modifications.

1. Introduction

Neonicotinoids are the most important class of synthetic insecticides in crop protection in the past decades. They represented 28.5% of global market for insecticides and 80% of seed treatment sales in 2011 [1]. Applied into the soil or to the seed, neonicotinoids are taken up *via* the roots, are distributed in the plant and give consistent and long-lasting control of sucking insect pests such as aphids, whiteflies, planthoppers, some micro lepidoptera and a number of coleopteran pest species [2]. However, due to similar modes of action of neonicotinoids, the problems of resistance and cross-resistance have become an increasing concern [3–5]. Previous studies reported that some species showed more than 100-fold resistance to imidacloprid (**1**, Fig. 1) [3,5]. Therefore, in order to combat current resistance and prevent further development of resistant strains, there is an urgent need to develop novel classes of neonicotinoids [6,7].

Bicyclic pyridone scaffolds are ubiquitous in a lot of biologically active compounds and natural products [8–10]. Some of them possess a broad range of biological properties, including insecticidal [11], antibacterial [8,12], anticancer [13] and anti-HIV activities [14,15]. Hence, the synthesis of tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one is a valuable strategy for discovering new bioactive compounds [11]. Reactions of 4-(substituted benzylidene)-2-phenyloxazole-5-ones with heterocyclic ketene aminals *via* aza-ene reaction have been applied for the creation of diverse heterocycles [16]. However, such aza-ene reaction with *β*-nitroenamines is scarcely reported.

For neonicotinoids, the coplanar system between the electronegative pharmacophore (=CNO_2 or =NNO_2) and guanidine–amidine moiety extends the conjugation and facilitates negative charge (δ^-) flow toward the tip, enhances binding affinity with novel nicotinic acetylcholine receptors (nAChRs), and has been proven as an important pharmacophore [17]. In previous studies, 2-chloro-5-((2-(nitromethylene)imidazolidin-1-yl)methyl)pyridine (*β*-nitroenamines 6-Cl-PMNI) was used intensively as starting materials due to it containing two reactive nucleophilic sites as shown in Fig. 2. (A) α-Carbon atom of the nitromethylene group could be attack by electrophilic agents; (B) *β*-secondary amine group in imidazolidine also has good reactivity. The obtained compounds with the electronegative pharmacophore (=CNO_2), such as Paichongding, IPP152201, and cycloxaprid, exhibited excellent insecticidal activity [18–22], which encouraged us to further explore structural modification and diversification of these neonicotinoids derivatives.

Enlightened by all of intriguing reasons above, we examined the reaction behavior of *β*-nitroenamine 6-Cl-PMNI with 4-(substituted benzylidene)-2-phenyloxazole-5-ones. Herein, a series of

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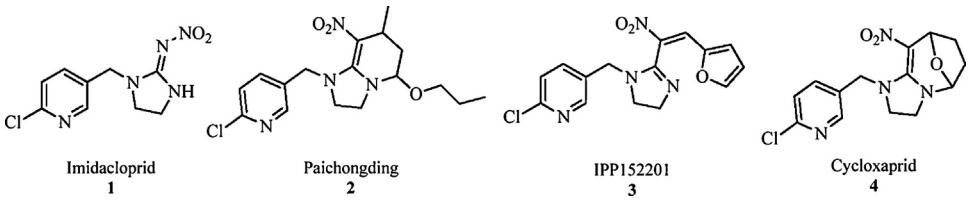

Fig. 1. Imidacloprid and representative neonicotinoids discovered in our group.

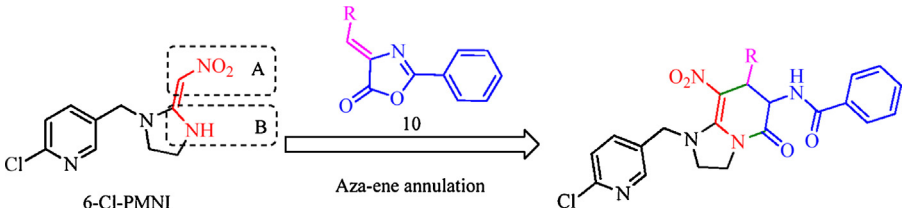

Fig. 2. Design strategy of tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one derivatives.

tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one derivatives were designed and synthesized. Their insecticidal activities against cowpea aphids (*Aphis craccivora*) and brown planthopper (*Nilaparvata lugens*) were evaluated.

2. Experimental

2.1. Chemistry

Reagents and solvents were obtained from commercial sources and used without further purification. Melting points (mp) were determined on a Büchi Melting Point B540 and were uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker AM-400 instruments in DMSO-d_6 solvent (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, and ^{19}F NMR at 376 MHz). Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were determined on a MicroMass GCT CA 055 instrument. All MS experiments were performed using electrospray ionization (ESI) in positive ion mode. Reaction progress was determined by thin layer chromatography (TLC) analysis on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

Synthesis of benzoyl glycine **8**: Glycine (0.1 mol) was dissolved in 75 mL of 10% sodium hydroxide solution. To this, benzoyl chloride (**7**, 0.115 mol) in five portions was added with stirring until benzoyl chloride completely reacted. The solution was transferred to beaker and rinsed the conical flask with a little water. A few gram of crushed ice was added in the solution. Then concentrated hydrochloric acid was added slowly with stirring until the mixture was acidic. The crystalline precipitate of benzoyl glycine was filtered, washed with carbon tetrachloride and then with cold water. The solid product was collected, dried and recrystallized in boiling water. Yield: 90%; mp: 85.1–85.6 °C.

General procedure for preparation of **9a–9r**: A mixture of aldehyde (0.1 mol), benzoyl glycine (**8**, 0.1 mol), acetic anhydride (0.3 mol) and anhydrous potassium acetate (0.1 mol) was heated to 90 °C till the mixture liquefied. Then the reaction mixture was stirred on an oil bath and monitored by TLC. After 3 h, to this 10 mL of ethanol was added slowly and allowed the mixture to stand overnight at room temperature. The crystalline product was separated by filtration, washed with 5 mL of ice-cold alcohol and then finally washed with 5 mL of boiling water and recrystallized using suitable solvent.

General procedure for preparation of **10a–10r**: A solution of 4-(substituted benzylidene)-2-phenyloxazole-5-ones (**9a–9r**, 8.0 mmol), 6-Cl-PMNI (10.0 mmol), and hydrobromic acid (10 mmol) in 50 mL acetonitrile at refluxing temperature was stirred. The reaction progress was monitored by TLC. After completion of the reaction, the organic solvent was extracted thoroughly with CH_2Cl_2 (30 mL × 3), washed with water, and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/acetone (4:1, v/v) to afford target products **10a–10r**.

Physical and spectroscopic characterization data of compounds **10a–10r** were given in Supporting information.

2.2. Biological assay

Bioassays were performed on representative test organisms grown in the laboratory. The bioassay was repeated at (25 ± 1) °C according to statistical requirements. All compounds were dissolved in *N*,*N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg L^{-1}) to obtain a series of concentrations of 500.0, 100.0 mg L^{-1} and others for bioassays. For comparative purposes, avermectins and cycloxaprid as control was tested under the same conditions.

Insecticidal test for cowpea aphids (*A. craccivora*): The activities of insecticidal compounds against cowpea aphids were tested by leaf-dip method. The leaves of the horsebean plant with 40–60 apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s and the excess solution was sucked out with filter paper, and the burgeons were placed in the conditioned room ((25 ± 1) °C, 50% RH). Water containing Triton X-100 (0.1 mg L^{-1}) was used as a control. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions and the data were adjusted and subjected to probit analysis as before.

Insecticidal test for brown planthopper (*N. lugens*): The insecticidal activity against brown planthopper was tested by foliar application. Rice seedlings were placed on moistened pieces of filter paper in Petri dishes. The dishes were infested with third instar larvae and then sprayed with the compound solutions (2.5 mL) using a Potter spray tower (pressure, 5 lb $(in^2)^{-1}$; settlement, 4.35 mg $(cm^2)^{-1}$). Samples were placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subject to probit analysis as before. The results of bioassay are depicted in Table 1.