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Original article

Design, synthesis, and insecticidal bioactivities evaluation of pyrrole- and dihydropyrrole-fused neonicotinoid analogs containing chlorothiazole ring

Hong-Feng Shen [a], Xi Chen [a], Pin Liao [a], Xu-Shen Shao [a,b], Zhong Li [a,b], Xiao-Yong Xu [a,b,*]

[a] Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China
[b] Shanghai Collaborative Innovation Center for Biomanufacturing Technology, Shanghai 200237, China

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ABSTRACT

Chlorothiazole ring, as a substituted heterocycle, frequently occurred in structures of various insecticides, and brought positive effect on bioactivity. In purpose to find novel neonicotinoids, a series of pyrrole- and dihydropyrrole-fused neonicotinoid analogs containing chlorothiazole ring were synthesized for the first time. Results of the following biological assays showed that compounds **5a–c** achieved good insecticidal activity against *Aphis craccivora*, and compound **5h** exhibited good activity against *Nilaparvata lugens*.

1. Introduction

Since the discovery of imidacloprid [1], the neonicotinoids have been widely used for crop protection and veterinary pest control [2–4]. However, they are now facing a big challenge arising from growing resistance [5–7] and severe bee toxicity [8–10]. On that account, agrochemists have made persistent efforts for the development of novel neonicotinoids which could be more effective and environmental-friendly. In recent years, Li *et al.* reported pyrrole-fused neonicotinoids [11], hydropyridine-fused neonicotinoids [12–14] and oxabridged neonicotinoids [15,16], in all of which the nitro group was located in the same direction as the aromatic heterocycle (*cis*) [17], and achieved good to excellent insecticidal activity.

Thiazole was a common structural motif in a large number of insecticides, for example, hexythiazox [18], nemathorin [19]. The hotspot on thiazole can be partly ascribed to the capacity in promoting bioactivity, widening insecticidal spectrum and reducing mammal toxicity. Especially in neonicotinoids, 2-chloro-5-thiazole ring not only acted as an important role in binding to target, but also benefit to improve selectivity [20–23]. On this basis, a series of pyrrole-fused new neonicotinoids containing chlorothiazole ring were synthesized, expecting to get excellent results in insecticidal activity and spectrum.

2. Experimental

2.1. Chemistry

The general synthetic methods for compounds **5a–j** and **6a–c** are shown in Scheme 1. Unless otherwise noted, reagents and solvents used were from commercial source.

General synthetic procedure for **4a**: Starting from 2-chloro-5-chloromethyl-thiazole **1**, intermediates **2**, **3** were obtained in good yields according to reported procedures [11]. Reactant **3a** (2.6 g, 10 mmol) was dissolved in 40 mL dichloromethane, then an aqueous solution of methylglyoxal (2.7 g, 12 mmol, 32%) was added dropwise. The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After 45 min, the precipitate was filtered and washed with acetone to afford the white solid **4a** (2.52 g, 76%).

General synthetic procedure for **5a–f**: Compound **4a** (0.664 g, 2 mmol) was dissolved in 30 mL alcohol or ketone, then anhydrous aluminum chloride (0.026 mg, 0.2 mmol) was added. After stirred at room temperature for 45 min, most of the solvent was removed before adding 30 mL water and then extracted three times with

* Corresponding author at: Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China.
E-mail address: xyxu@ecust.edu.cn (X.-Y. Xu).

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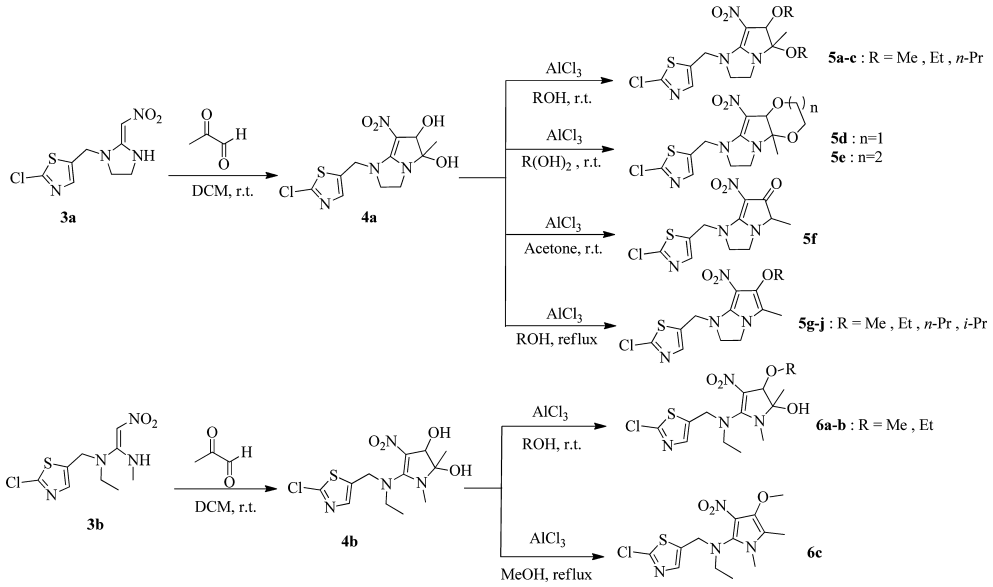


Scheme 1. Synthetic routes for pyrrole- and dihydropyrrole- fused neonicotinoid analogs.

dichloromethane, 20 mL for each. The organic layer was combined, dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the desired products **5a**–**f**.

General synthetic procedure for **5g**–**j**: Compound **4a** (0.664 g, 2 mmol) was dissolved in 30 mL alcohol, then anhydrous aluminum chloride (0.026 mg, 0.2 mmol) was added under reflux. The process was monitored by TLC. After completion, most of the solvent was removed, then extracted three times with dichloromethane, 20 mL for each. The organic layer was combined, dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the desired products **5g**–**j**.

General synthetic procedure for **6a**–**c**: Compound **3b** (0.828 g, 3 mmol) was dissolved in 30 mL dichloromethane, then an aqueous solution of methylglyoxal (0.810 g, 3.6 mmol, 32%) was added dropwise. After stirred at room temperature for 45 min, 30 mL water was added, went on stirring for another 15 min before extracted with dichloromethane for five times, 20 mL for each. The organic layer was combined, dried with anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product **4b**. Compound **4b** (0.696 g, 2 mmol) was dissolved in 30 mL alcohol, then anhydrous aluminum chloride (0.026 mg, 0.2 mmol) was added. After stirred at room temperature (**6a**–**b**) or reflux (**6c**) for 45 min, most of the solvent was removed before adding 30 mL water and then extracted three times with dichloromethane, 20 mL for each. The organic layer was combined, dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give the desired products **6a**–**c**.

The structures identification data of target compounds are listed in Supporting information.

2.2. Biological assay

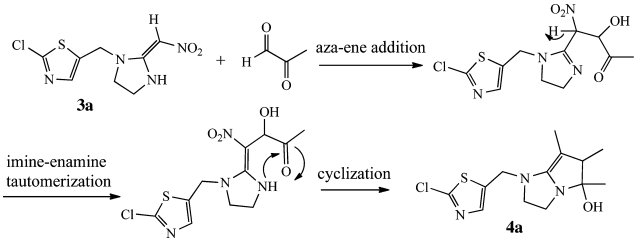
All bioassays were performed on representative test organisms grown in the laboratory. The bioassay was repeated at (25 ± 1) °C according to statistical requirements. All compounds were dissolved in *N*,*N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg/L) to obtain a series of concentrations of 500.0, 100.0, 20.0 mg/L and others for bioassays. The insecticidal activity of the synthetic compounds against *Aphis craccivora* and *Nilaparvata lugens* was tested according to our previous reported procedure [12,15,24].

3. Results and discussion

3.1. Synthesis

β-Nitro enamine intermediates **3a**–**b** were good electrophilic reagents by reason of highly polarized push–pull ethylene systems. With strong electron-withdrawing group, β-nitro, and electron-donating group, amino group, on different ends, the alkene double bond turned to be polarized owing to electron-transfer delocalization. So that, when methylglyoxal was added as an electrophile with two electrophilic sites of carbonyl, addition reaction came up on both carbonyls, leading to the formation of the cyclized products **4a**–**b** (Scheme 2, illustrated as **4a**).

Catalyzed by anhydrous aluminum chloride, dihydroxy-substituted products **4a**–**b** were etherified by different alcohols either at room temperature or under reflux. If etherification occurred at room temperature, dietherified compounds were obtained using **4a** as the substrate. However, for **4b**, only one of that two hydroxyl groups was successfully etherified to form **6a** or **6b** in different alcohols under the same condition. Moreover, as **4b** were refluxed in methanol, elimination took place at the same time to form aromatized compound **6c**.



Scheme 2. Synthetic mechanism of the dihydroxyl dihydropyrrole fused neonicotinoid intermediate.