Chinese Chemical Letters 25 (2014) 1017–1020

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis, insecticidal activity and molecular docking study of clothianidin analogues with hydrazide group

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ARTICLE INFO

Article history:
Received 18 December 2013
Received in revised form 6 March 2014
Accepted 7 March 2014
Available online 27 March 2014

Keywords:
Clothianidin analogues
Hydrazide group
Insecticidal activity
Molecular docking

ABSTRACT

A series of novel neonicotinoid analogues were designed and synthesized by introducing a hydrazide group into clothianidin. Their structures were confirmed by IR, ^{1}H NMR, and HRMS (ESI). Preliminary bioassay showed that some compounds, **5b** and **5g**, exhibited good activity against soybean aphids (*Aphis glycines*) at 100 mg L^{-1}. In addition, molecular docking with receptor was carried out to explain their different activity from clothianidin.

1. Introduction

Neonicotinoid insecticides (NNs), exemplified by imidacloprid, have agonistic effects on the insect nicotinic acetylcholine receptor (nAChR) [1,2], which makes this kind of insecticide particularly effective in controlling sap-feeding pests and relatively safe toward mammals [3–6]. These NNs are widespread and account for one-fifth of the global insecticide market [7–9]. However, during the past decade, increases in resistance and cross resistance were observed in a range of species after their frequent applications in the field [10–13]. Further, it was reported that NNs have toxicity towards honey bees, which also limited their applications [14]. Hence, it is necessary to design and screen novel insecticidal lead compounds with low resistance and high safety.

Most structure optimizations of NNs are based on cyclic neonicotinoid insecticides [15–18], but few studies have been focused on the structural modification of acyclic NNs, such as clothianidin. In addition, diacylhydrazine compounds have been widely used as one of the most important insect growth regulators [19,20], and the hydrazide group has also been proved to be a useful section in the scaffold of active insecticides [21,22]. Encouraged by this, we hereby introduced a new structure developing strategy, using clothianidin as the lead compound, and a series of novel neonicotinoid derivatives similar to diacylhydrazine were designed by introducing a hydrazide group into clothianidin. Their insecticidal activity against soybean aphids (*Aphis glycines*) was evaluated at different concentrations. Furthermore, the interactions between these new compounds and nAChR were also investigated by molecular docking.

2. Experimental

Melting points of all compounds were determined on an X-5 binocular microscope (Fukai Instrument Co., Beijing, China), and were not corrected. ^{1}H NMR spectra were recorded on Bruker AM-300 (300 MHz) spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS Varian 7.0T FTICR-MS instrument. All the reagents were obtained commercially and used after further purification. Column chromatography purification was carried out by using silica gel.

2.1. General procedure for synthesis of compounds 5a–5l

A solution of **3** (10.0 mmol) and hydrazine hydrate (12.0 mmol) in methanol (20 mL) was refluxed for 0.5 h. Then the mixture was concentrated and the residue was purified by recrystallization with ethanol to afford the pure compound **4**. Then a solution of **4** (5.0 mmol), DMAP (0.25 mmol) and TEA (7.5 mmol) in

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http://dx.doi.org/10.1016/j.cclet.2014.03.026

dichloromethane (15 mL) was cooled to −5 to 0 °C, and acyl chloride (7.5 mmol) was added dropwise. After that, the mixture was stirred at room temperature for 6 h. After being quenched by water (5 mL), the mixture was filtered, and the precipitate was washed with dichloromethane then purified by recrystallization with ethanol to afford the pure products **5a–5l**.

2.2. Insecticidal test for soybean aphids (A. glycines)

The activities of the insecticidal compounds against soybean aphids were tested by the leaf-dip method. Horsebean plant leaves with 40–60 apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.05 mg L^{-1}) for 5 s, the excess dilution 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 (0.05 mg L^{-1}) was used as a control, and clothianidin was used as positive control at the same time. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions and the data was subjected to probit analysis [23].

2.3. Experimental protocol of docking study

The highly active compound **5g** was chosen for investigation of the ligand–protein interactions in detail with clothianidin as a contrast, and a Surflex-Dock was used to carry out the molecular modelling study. The crystal structure of the *Aplysia californica* acetylcholine binding protein (*Ac*-AChBP) complexed with thiacloprid (PDB: 3C84) was used as the template to construct the models [24,25]. The receptor was prepared for docking by the addition of hydrogen atoms and the removal of cocrystallized molecules. The low energy conformation of each neonicotinoid analogue was optimized by a MMFF94 force field and MMFF94 charges as an initial docking conformation.

Table 1
Insecticidal activity of target compounds **5a–5l** against soybean aphid (*Aphis glycines*).

Compd.	R^1	R^2	Mortality (%) at different concentrations (mg L^{-1})		
			500	100	20
5a	F-Ph	Me	41.2	nt[a]	nt
5b	Cl-Pyr	Me	91.5	82.2	53.4
5c	Cl-Pyr	Et	77.6	nt	nt
5d	Cl-Pyr	*n*-Pr	66.3	nt	nt
5e	Cl-Pyr	*n*-Bu	62.7	nt	nt
5f	Cl-Pyr	*n*-Hep.	48.5	nt	nt
5g	Cl-Thy	Me	94.5	83.9	51.9
5h	Cl-Thy	Et	83.0	44.5	19.8
5i	Cl-Thy	*n*-Pr	75.1	nt	nt
5j	Cl-Thy	*n*-Bu	65.3	nt	nt
5k	Cl-Thy	*n*-Hep.	50.4	nt	nt
5l	Cl-Thy	4-Cl-Ph	54.2	nt	nt
clothianidin	–	–	100.0	100.0	92.6

[a] nt = not tested.

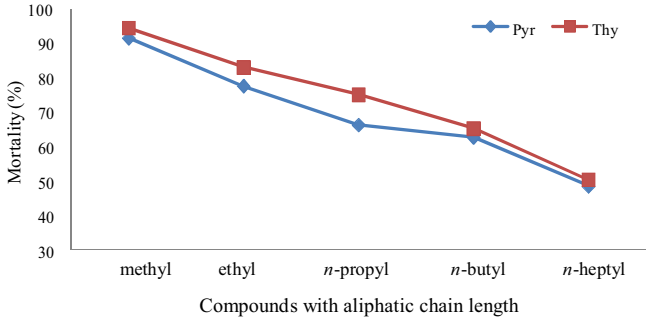
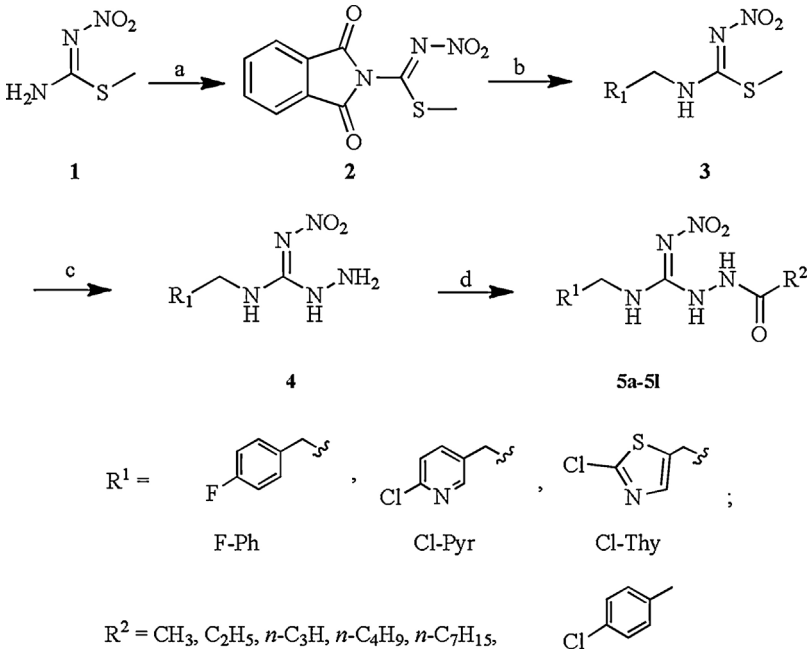


Fig. 1. Effect of the number of carbon atoms on the insecticidal activity.

3. Results and discussion

The synthetic route of the target compounds (**5a–5l**) was summarized in Scheme 1. The starting material *S*-methyl-*N*-nitroisothiourea **1** was prepared by the literature method [26]. Compound **2** was obtained in high yield by reaction of **1** with phthaloyl dichloride at 0 °C to room temperature. Then it was reacted with benzylamine and purified by alcohol to afford **3**.



Scheme 1. Synthetic route for neonicotinoids containing hydrazide group. Reagents and conditions: (a) phthaloyl dichloride (1.5 equiv.), pyridine, 0 °C for 1 h; (b) benzylamine (1.2 equiv.), CH_2Cl_2, 0 °C for 1 h, r.t. for 3 h; (c) hydrazine hydrate (1.2 equiv.), CH_3OH, reflux for 0.5–1 h; (d) acyl chloride (1.5 equiv.), Na_2CO_3 (1.5 equiv.), DMAP (0.5 equiv.), CH_2Cl_2, 0 °C for 0.5 h, r.t. for 6–8 h.