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Original article

Design, synthesis and insecticidal activities of novel 1-substituted-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide derivatives

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ABSTRACT

A series of novel 5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide derivatives (**6a–6n**, **7a**, **7b**, and **8a-8f**) were synthesised by placing the amide bond at the 4-position of the pyrazole ring. These derivatives differed from the structure of chlorantraniliprole analogues with the amide bond at the 5-position of the pyrazole ring. Preliminary bioassay results revealed that a few title compounds exhibited good insecticidal activities against lepidopteran pests, such as *Plutella xylostella*, *Mythimna separate*, *Heliothis armigera*, and *Ostrinia nubilalis*. Some title compounds also elicited broad-spectrum insecticidal activities against dipterous insects including *Culex pipiens pallens* after altering the amide position. Similar to pyrazole-5-carboxamide analogues, compounds **6b** and **6e** showed 100% insecticidal activity against *P. xylostella*, *C. pipiens pallens*, and *M. separate* at concentrations of 200, 2, and 200 μg/mL, respectively. This finding suggested that 5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide derivatives are potential alternative insecticides for management of agriculture pests.

1. Introduction

Agricultural pests, one of the most serious threats in crop production, have caused huge economic losses annually. Chemical control is used for crop protection because of its high efficiency and accessibility. The pyrazole-5-carboxamide compound chlorantraniliprole exhibits excellent insecticidal activities against lepidopteran pests and has been successfully commercialised. Studies showed that chlorantraniliprole acts on ryanodine receptors (RyRs) [1–3]. Numerous researchers have focused on research and development of alternative insecticides based on the structure of chlorantraniliprole because of its effective bioactivity towards insects. Fig. 1 shows that the structure chlorantraniliprole is modified and optimised based on the following three aspects: part A, substituted benzene ring or heterocyclic ring [4,5]; part B, different substituent instead of amines [6]; part C, bridging group instead of amide [7], the modification of pyridyl pyrazole moiety [8] and the change of diamide to diphenic amide [9]. To date, numerous pyrazole-5-carboxamide analogues were designed and reported with satisfactory insecticidal activities. However, resistance risks have gradually emerged as a consequence of continuous application of this pesticide [10,11]. Therefore, research and development of alternative insecticide agents to reduce resistance risks remains a challenging task in pesticide science. Among all chlorantraniliprole derivatives reported, most of the amide bond linked to the pyrazole ring are found on the 5-position; however, pyrazole-4-carboxamide derivatives have been rarely investigated [12].

In this study, a series of novel 5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide derivatives were designed and synthesised with the amide bond at the 4-position of the 5-trifluoromethyl-1*H*-pyrazole ring to analyse insecticidal activity (Fig. 1). Within these molecules, the trifluoromethyl group and 2-chloropyridine moiety (or phenyl ring) are settled at the 5-position and 1-position of the pyrazole ring, respectively. Acylhydrazone sub-structure (B_2) was introduced for comparison of amide moiety (B_1) and embedded into the structure of chlorantraniliprole to extend molecular scope and obtain highly efficient target molecules. All target compounds were bioassayed against *Plutella xylostella*, *Culex pipiens pallens*, *Mythimna separata*, *Heliothis armigera*, and *Ostrinia nubilalis*. Preliminary insecticidal bioassay results showed that a few

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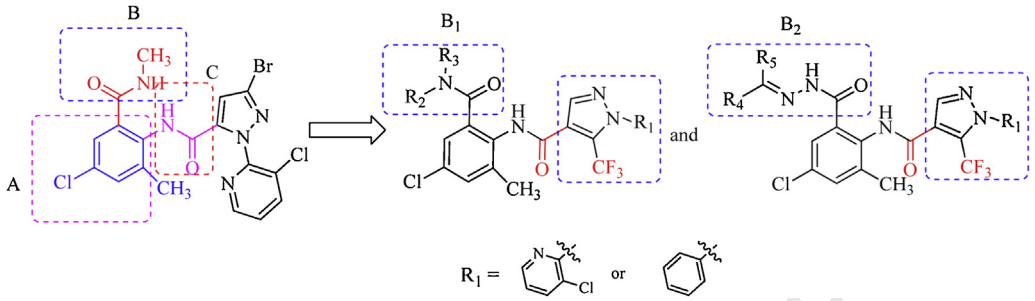

Fig. 1. Structure of modified and optimised chlorantraniliprole.

compounds exerted good activities against *P. xylostella*, *C. pipiens pallens*, and *M. separate*.

2. Experimental

Melting points of the compounds were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL-ECX-500 spectrometer. Chemical shifts were reported in parts per million (ppm) down field from TMS with the solvent resonance as internal standard. Coupling constants (*J*) were reported in Hz and referred to apparent peak multiplications. Mass spectral studies were conducted on an Agilent 5973 organic mass spectrometer. Elemental analysis was performed using Vario-III CHN analyser. IR spectra were recorded on a Bruker VECTOR 22 spectrometer.

The synthesis route for title compounds **6a–6n**, **7a**, **7b** and **8a–8f** is shown in Scheme 1. Intermediates **1** to **3** were prepared through previously reported procedure using ethyl 4,4,4-trifluoro-3-oxobutanoate [13–15]. Key intermediates **4** were prepared by cyclisation reaction from **3** and 2-amino-5-chloro-3-methylbenzoic acid in the presence of pyridine and methylsufonyl chloride [3]. Intermediates **5** were prepared by treating intermediates **4** with 80% hydrazine hydrate according to the reported method [16].

2.1. General procedure for preparation of *6a–6n*

Substituted amine was added into a solution of intermediate **4** (0.68 mmol) in 5 mL of acetonitrile. The mixture was stirred at room temperature, and TLC was used to monitor the reaction. Finally, pure compounds (**6a**–**6n**) were obtained by recrystallising the crude products in ethanol.

2.2. General procedure for preparation of *7a* and *7b*

A mixture of 40% methyl hydrazine (9.9 mmol) in THF (10 mL) was added gradually into the solution of intermediate **4** (4.9 mmol), dissolved in THF (10 mL) and then stirred at room temperature for 2 h. TLC was used to monitor the reaction. The mixture was filtered and recrystallised in ethanol to obtain title compounds **7a** and **7b**.

2.3. General procedure for preparation of title compounds *8a–8f*

Different ketone and aldehyde (or hemiacetal) (1.5 mmol) was added to a stirred solution of intermediate **5** (1.0 mmol) in 5 mL of ethanol. The mixture was refluxed for 30 min, filtered and recrystallised in a mixture of ethanol and DMF (1:1 in volume) to obtain pure compounds **8a–8f**.

Physical and spectroscopic characterisation data for title compounds **6a–6n**, **7a**, **7b** and **8a–8f** can be found in Supporting information, and the representative data for **6e** are shown below.

N-(4-chloro-2-(isopropylcarbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (**6e**):

White solid, yield 47%, m.p. 234~235 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.17 (s, 1H, NH), 8.66 (d, 1H, J = 4.6 Hz, pyridine H), 8.46 (s, 1H, pyrazole H), 8.39 (d, 1H, J = 8.0 Hz, benzene H), 8.23 (d, 1H, J = 7.5 Hz, pyridine H), 7.82-7.79 (m, 1H, pyridine H), 7.53 (s, 1H, benzene H), 7.35 (s, 1H, NH), 3.99-3.93 (m, 1H, CH), 2.27 (s, 3H, $PhCH_3$), 1.08 (s, 3H, CH_3), 1.07 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.5, 158.8, 148.3, 147.9, 141.4, 140.9, 139.3, 137.4, 132.6, 132.0, 131.7, 131.3, 128.6, 128.4, 126.0, 122.8, 120.8, 120.6,118.5, 41.4, 22.6, 18.2; IR (KBr, cm^{-1}): ν 3244.2, 3066.8, 2974.2, 2931.8, 1662.6, 1635.6, 1558.4, 1506.4, 1436.9, 1157.2, 867.9; MS (ESI): *m/z* 500 [M+H]+, 522 [M+Na]+; Anal. Calcd ($C_{21}H_{18}Cl_2F_3N_5O_2$): C, 50.41; H, 3.63; N, 14.00. Found: C, 50.25; H, 3.52; N, 13.87.

2.4. Insecticidal test

All bioassays were performed on test organisms reared in the laboratory and repeated at 25±1 °C according to statistical requirements. Mortalities were corrected using Abbott's formula. Evaluations were based on a percentage scale (0 = no activity and 100 = complete eradication) at intervals of 5% [17–22].

3. Results and discussion

3.1. Synthesis

As shown in Scheme 1, compound **4** is the key intermediate for the synthesis of title compounds and was prepared by **3** and 2-amino-5-chloro-3-methylbenzoic acid in the presence of pyridine and methylsufonyl chloride. An 89% yield could be obtained with the temperature at -5 °C. Then the reaction of **4** with substituted amines gave target compounds **6a–6n** with yields of 47% to 93%. Compounds **7a** and **7b** were synthesised by refluxing **4** and 40% methyl hydrazine. Compounds **8a–8f** containing the acylhydrazone sub-structure were prepared *via* the reaction of intermediate **5** and ketones, aldehydes or hemiacetal in ethanol, with the yield ranging from 70% to 90%.

3.2. Insecticidal activity

Preliminary insecticidal activity of the title compounds against five kinds of pests is shown in Table 1. Commercial insecticides such as chlorantraniliprole, avermectin or hexaflumuron were selected as positive controls. As indicated in Table 1, most of the target compounds exhibited good insecticidal activities against *P. xylostella* at 500 μg/mL. Similar to chlorantraniliprole and avermectin under the same conditions, compounds **6a**, **6b** and **8a** showed 100% activity against *P. xylostella* at 200 μg/mL. Similar to hexaflumuron, all the tested compounds exhibited 100% activity at

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