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Report

synthesis design, anthranilic diamides, insecticidal activity, RyRs, Structure–activity relationships

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Synthesis and Insecticidal Evaluation of Novel Anthranilic Diamides Derivatives Containing 4-Chlorine Substituted *N*-Pyridylpyrazole

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Summary of main observation and conclusion To search for potent insecticides targeting at ryanodine receptors (RyRs), a series of novel anthranilic diamides analogs containing 4-chlorine *N*-pyridylpyrazole were designed and synthesized. Their insecticidal activities were evaluated and the preliminary structure-activity relationships (SARs) were discussed. The insecticidal results showed that some of the compounds（**8a-8h,8m,8n**）exhibited good larvicidal activities against oriental armyworm at 2.5 mg·L^{-1} , and compound **8m** possessed 60 % insecticidal activity at 0.5 mg·L^{-1}. For diamondback moth, **8m** exhibited better activity than Chlorantraniliprole at a hundred fold preference. The calcium imaging technique experiment results suggested that compound **8m** could increase the intracellular [Ca^{2+}]$_i$, and with the neurons preincubated experiment, the results confirmed that the target of this series of compounds could be RyRs in the central larvae neurons of oriental armyworm. The results indicated that compound **8m** could respond as a potential modulator of the insect ryanodine receptor.

Background and Originality Content

The frequent application of traditional insecticides has generated growing concern over a series of problems, such as resistance,[1] environmental pollution and health risks.[2] To tackle these problems, there is an urgent requirement to develop broad-spectra and ultra efficient insecticidal compounds for pest managements which could guarantee natural and harmonious development.[3] It was reported that pyrazole-related compounds[4,5] played a critical role in the pesticide field. And as the representative of pyrazole-related compounds, diamide insecticides, act selectively on insect ryanodine receptors,[6-8] leading to the intermittent release of Ca^{2+} and finally causing insects starving to death, such as Chlorantraniliprole (**Fig. 1**, **A**) and Cyantraniliprole,[9,10] (**Fig. 1**, **B**). Therefore, it is regarded as a promising target for ryanodine receptors in the design of environment-friendly pesticides in the future.

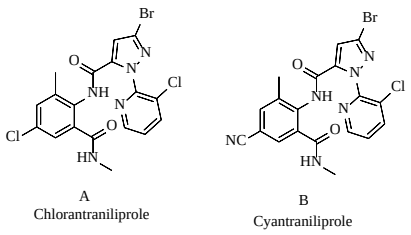


Figure 1. The structure of Chlorantraniliprole and Cyantraniliprole

Many research groups have devoted considerable efforts to a number of structural modifications since the introduction of diamide insecticides into the world market to date. Most of the modifications were mainly aimed at the following three parts: the aliphatic amide moiety **1**,[11-14]] the amide bridge moiety **2**[15-18] and the *N*-pyridylpyrazole moiety **3**.[19-23] (**Fig 2**, **C**) It is well acknowledged that the introduction of halogens into molecule has been regarded as the effective method for pesticide designs due to their chemical and biological characteristics.[24,25] For example, Xu *et al.* reported that 3,4-dihalopyrazole amide structure possessed a slightly higher insecticidal activity against diamondback moth than Chlorantraniliprole,[26] indicating that the 4-position of pyrazole moiety substituted with chlorine group could improve the bioactivity against diamondback moth. Tetrachlorantraniliprole (SYP-9080), a novel anthranilic diamides insecticide, were launched in 2014 which had extra chlorine substituted in the benzene ring.[27] Besides, some molecules bearing fluorine and fluorinated functional groups have been widely applied in pharmaceutical and agrochemical chemistry.[28,29] The introduction of trifluoromethyl substituent is often considered as an efficient strategy in the design of bioactive chemicals owing to great changes in their physicochemical and biological properties, such as enhancement of binding affinity, lipophilicity and so on.[30-32] For example, penthiopyrad,[33] as a novel fungicide, has a positive effect on the botrytis cinereal and powdery mildew, in addition to basidiomycete. Celecoxib[34] acts as an anti-inflammatory as well as antibacterial agent. Given the above facts, trifluoromethyl and chlorine group were brought into the pyrazole moiety to develop highly effective pesticides.

In this paper, a series of novel 3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide derivatives (**Figure 2**, **8a-8n**) were synthesized with the chlorine at the 4-position and their insecticidal activities were evaluated. Meanwhile, the preliminary structure-activity relationships (SARs) was explored, and the mode of action was

conducted.

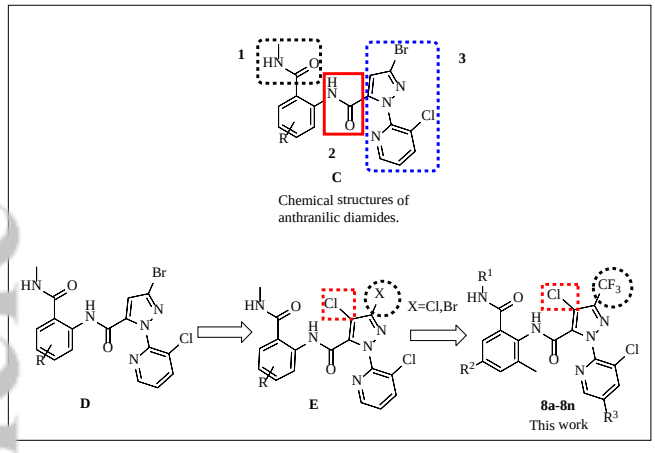
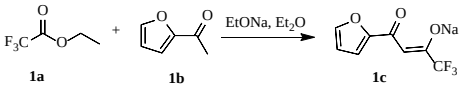


Figure 2. Design of the title compounds

Results and Discussion

Synthesis

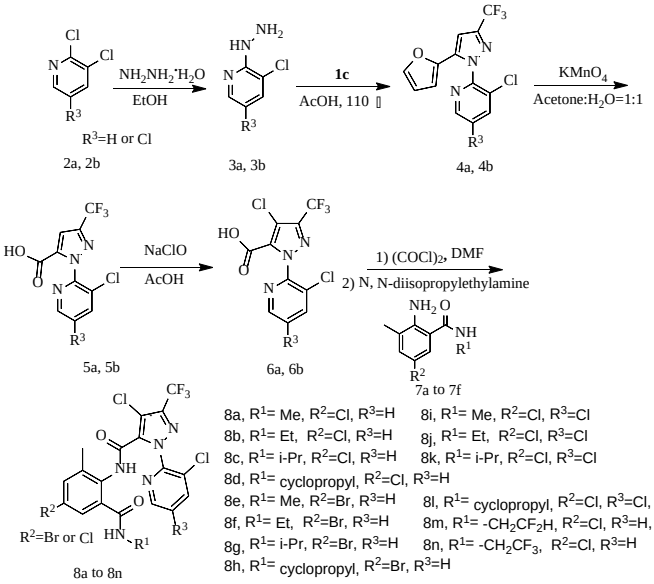
From Scheme 1, compound **1c** was synthesized by the condensation of ethyl trifluoroacetate(**1a**) with 2-acetylfuran(**1b**).[35] The synthetic route for the title compounds **8a–8n** was shown in Scheme 2.[36-38] The final products were prepared by a simple and convenient method, provoking the substitution reaction of 2, 3-dichloropyridine with hydrazinium hydroxide to get **3a**. By treating the intermediate **3a** and compound **1c** in acetic acid compound 4a was prepared, which was used directly into the next step to gain the key intermediate **5a**. Compound **5a** was added to NaClO in AcOH with the reported method in previous literature [39] to yield **6a**. The title compounds were obtained by the condensation reaction of compounds **6a**(**6b**) with**7a-7f**.[40]



Scheme 1. Synthesis of compound **1c**

Initially, when sulfuryl chloride (SO_2Cl_2) was used, the desired compound **6** could not be obtained. It was postulated that the heterocyclic ring of 3-(trifluoromethyl)-1*H*-pyrazole was lack of electrons, which resulted in the failure of the attack of chloride cation. Later, by using the sodium hypochlorite in AcOH, compound **5** was gained with good yields.

In the ^{1}H NMR spectra, the active proton signals of the amide moieties Ph-NH-CO- were observed at δ 10.49-10.55 in DMSO-d_6 and δ 9.95-9.99 in $CDCl_3$ and -Ph-CONH- at δ 8.29-8.56 in DMSO-d_6 and δ 8.46 in $CDCl_3$. In the ^{13}C NMR spectra, the signals of trifluoromethyl group appeared approximately at 120 ppm with quartet.



Scheme 2. Synthesis of compounds **8a-8n**

Structure-activity relationship (SAR)

Larvicidal activity against *Mythimna separata* (*M. separata*)

The oriental armyworm, *M. separata*, is an economically important and common Lepidopteran pest of cereal crops. The larvicidal activities of target compounds **8a-8n** and Chlorantraniliprole against *M. separata* were shown in Table 1. The results indicated that most of the title compounds exhibited good insecticidal activity (100 %) at 2.5 mg·L^{-1}. When the concentration was reduced to 1 mg·L^{-1}, compounds **8a**, **8b**, **8c** and **8h** showed similar lethal rates–80 %, 85 %, 80 % and 80 %, respectively. It was noted that compound **8m** still had 100% larvicidal activity at 1 mg·L^{-1}. Furthermore, compound **8m** possessed inhibitive capacity (60 % pesticidal activity) at 0.5 mg·L^{-1}.

As seen from different alkyl groups in R^1 from Table 1, the sequence on larvicidal activity was CH_2CF_2H > Et ≈ i-Pr ≈ cyclopropyl ≈ Me. The activity of compound **8m** with fluorine atom in R^1 group was increased compared with title compound **8b**. It was speculated that R^1 group containing fluorinated substituents could be essential for the improvement of the larvicidal activity. Compounds **8a-8d** (**8e-8f**) had similar activities, which indicated that electronic effects of different groups at R^1 site had little influence on the insecticidal activity. To explore the effect of the R^2 group in the benzene on the pesticidal activities, compounds **8a**, **8b**, **8e** and **8f** were synthesized and evaluated for their insecticidal activity. The bioassay results manifested that the general sequence of the larvicidal activity was Cl ≈ Br (**8a** vs **8e**, **8b** vs **8f**, **8c** vs **8g**, **8d** vs **8h**).

The investigation of Cl group in R^3 site impact on the larvicidal activity was also conducted. The bioactivities of compounds **8i-8l** declined sharply in comparison with the corresponding compounds **8a-d** (**8a** vs **8i**, **8b** vs **8j**, **8c** vs **8k**, **8d** vs **8l**). These observations revealed that R^3 groups in the pyridine ring could have an important influence on the larvicidal activity, which was speculated that the introduction of Cl group might decrease insecticidal

bioactivity with the steric hindrance.

In Table **3**, the LC_{50} value of **8m** was 0.3360 mg·L^{-1}, which indicated that the larvicidal activity of **8m** was slightly lower than that of Chlorantraniliprole(0.1254 mg·L^{-1}).

Table 1. Insecticidal activities of title compounds **8a-8n** and Chlorantraniliprole against *M. separata*

Compd.	larvicidal activity (%) at conc. (mg·L^{-1})					
	25	10	5	2.5	1	0.5
8a	100	100	100	100	80	
8b	100	100	100	100	85	
8c	100	100	100	100	80	
8d	100	100	100	100	50	
8e	100	100	100	100	50	
8f	100	100	100	100	65	
8g	100	100	100	100	75	
8h	100	100	100	100	80	
8i	60					
8j	100	100	100			
8k	100	100	100			
8l	100	30				
8m	100	100	100	100	100	60
8n	100	100	100	100	45	
Control	100	100	100	100	100	100

Control= Chlorantraniliprole.

Table 2. Insecticidal activities of title compounds **8a-8n** and Chlorantraniliprole against *P. xylostella*

Compd.	larvicidal activity (%) at conc. (mg·L^{-1})						
	2	0.1	10^{-2}	10^{-3}	5×10^{-4}	5×10^{-5}	5×10^{-6}
8a	100	100	100	100	95	82	40
8b	90						
8c	100	100	100	88	70		
8d	90						
8e	100	100	100	97	85		
8f	90						
8g	100	94	85	70	43		
8h	90						
8i	70						
8j	70						
8k	100						
8l	30						
8m	100	100	100	100	100	100	80
8n	100	100	100	90	80		
Control	100	100	100	95	75		

Control= Chlorantraniliprole

Larvicidal activity against *Plutella xylostella* (*P. xylostella*)

To better study the insecticidal spectrums of these compounds, the larvicidal results of title compounds(**8a**-**8n**) for *P. xylostella* were summarized in Table 2. Some of the compounds exhibited excellent insecticidal activities. When the concentration of the tested compounds was at 0.01 mg·L^{-1}, the title compounds **8a**, **8c**, **8e**, **8m** and **8n** had similar larvicidal activities, equal to that of Chlorantraniliprole. Moreover, compound **8a** and **8m** possessed 95 % and 100 % bioassay activity at 5×10^{-4} mg·L^{-1}, respectively, indicating that their bioactivities were comparable to that of Chlorantraniliprole. It was observed that **8m** still gave a death rate of 80 % at the lower concentration of 5×10^{-6} mg·L^{-1}, which surpassed that of Chlorantraniliprole.

When the R^3 group was H, the general insecticidal trend was Cl > Br (**8a** vs **8e**, **8b** vs **8f**, **8c** vs **8g**, **8d** vs **8h**). From table 2, it was found that the activity of compound **8m** was higher than that of **8b** when the R^2 and R^3 was fixed. In Table **4**, the LC_{50} values of **8a and 8m** against *P. xylostella* correspondingly were 1.8×10^{-5} mg·L^{-1} and 3.7×10^{-6} mg·L^{-1}, lower than that of Chlorantraniliprole (LC_{50}, 1.0×10^{-4} mg·L^{-1}), implying that the larvicidal activity of the two compounds surpassed the bioactivity of Chlorantraniliprole.

For the *P. xylostella,* the pesticidal activity of compound **8i**-**8l** declined obviously compared with compound **8a-8d** at 2 mg·L^{-1}, and it was hypothesized that the introduction of the Cl group in the pyridine could probably decrease the electron density of the pyridine ring, causing a poor binding at the RyRs. When the R^2 site was substituted by Br or Cl group, the bioactivity results were similar, which demonstrated that the electronic effects on the improvement of bioactivity was slight.

Table 3. LC_{50} values of compound **8m** and chlorantraniliprole against *M. separata*

Compd.	*y* = a + b*x*	R	LC_{50}(mg/L)
8m	y=6.3521+2.8547x	0.9844	0.3360
chlorantraniliprole	y=8.1189+3.4587x	0.9655	0.1254

Table 4. LC_{50} values of compound **8a, 8m** and chlorantraniliprole against *P. xylostella*

Compd.	y = a + bx	R	LC_{50}(mg/L)
8a	y = 12.8964 + 1.6597x	0.9911	1.8×10^{-5}
8m	y = 14.0628 + 1.6694x	0.9895	3.7×10^{-6}
Chlorantra-niliprole	y = 11.2915 + 1.5391x	0.9673	1.0×10^{-4}

Mode of action

To explore the mechanism of the title compounds, we studied the impact of compound **8m** on the free Ca^{2+} concentration in the central neurons of third larva of *M. separata*. **Figure 3** presented the elevation of $[Ca^{2+}]_i$ versus recording time when the fluorescent loaded central neurons were treated with compound **8m**. No obvious change was observed for $[Ca^{2+}]_i$ in the cytoplasmic of central neurons after applying **8m** at 0.5 ppm. However, when the terminal concentration of **8m** was increased from 0.5 ppm to 5 ppm, $[Ca^{2+}]_i$ in the cytoplasmic domain increased to 103.65 ± 1.46 (n = 13), and these results indicated that the change elevation of $[Ca^{2+}]_i$ was in a concentration dependent manner(**Figure 3A**). Further experiments were also carried out to test the target. After the neurons were preincubated with 1μM Ryanodine about 5min, the $[Ca^{2+}]_i$ in the cytoplasmic kept being released for a long time (n=7) (**Figure 3B**). The results strongly suggested that the target of compound **8m** could be RyR in the test insect.

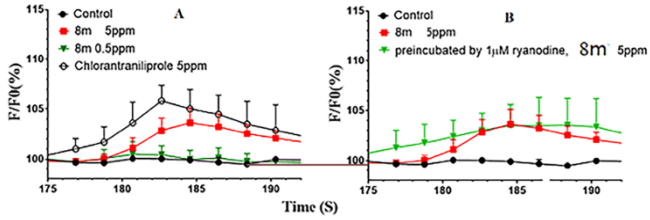


Figure 3. Effects of **8m** on $[Ca^{2+}]_i$ in the central neurons of *M. separata*, the central neurons of *M. separata* were dyed by loading with fluo-3 AM

Conclusions

In summary, **14** novel pyrazole-4-chlorine anthranilic diamide analogues were designed, synthesized and their insecticidal activities were evaluated against *M. separata* and *P. xylostellla*. Some title compounds showed good to remarkable activity against *M. separata* and *P. xylostellla.* It was noteworthy that **8a** and **8m** exhibited 40 % and 80 % larvicidal activity against *P. xylostellla* at 5×10^{-6} m·L^{-1} respectively and the LC_{50} of **8a** and **8m** for *P. xylostellla* were correspondingly were 1.8×10^{-5} mg·L^{-1} and 3.7×10^{-6} mg·L^{-1}, which were much more active than Chlorantraniliprole (LC_{50}, 1.0×10^{-4} mg·L^{-1}) . The calcium imaging technique experimental results demonstrated that the title compound **8m** could effectively modulate the insect calcium channel indeed in *M. separata*, implying that the modified compounds were the potent activators of the RyRs. It is believed that the preliminary results will provide useful information for further design of new RyRs activators in insecticidal research.

Experimental

Instruments and Materials.

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz using a Bruker AV 400 spectrometer (Bruker Co., Switzerland) in $CDCl_3$ (Heowns, Tianjin, China) or DMSO-d_6 (J&K Scientific, China) solution with tetramethylsilane as the internal standard, and chemical shift values were given in parts per million (ppm). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing TechInstrument Co., Beijing, China) and the temperature were uncorrected. Analytical thin layer chromatography was performed on silica gel GF254. Flash chromatography was performed with silica gel (200-300 mesh) (Energy Chemical, Shanghai, China). High-resolution mass spectrometry (HRMS) dates were obtained on a Varian QFT-ESI instrument.

Synthetic procedure for 6a, 6b[39]

To a solution of the compound (**5a** or **5b**, 0.685 mmol) in AcOH (5 mL) was added the sodium hypochlorite (1.20 mL, 1.71 mmol) dropwise at 10-13 ℃, then the mixture was stirred at room temperature overnight. The resulted mixture was concentrated under reduced pressure and the residue was added to H_2O (4 mL), acidated to pH= 1-2 with 6 N HCl. The mixture was filtered and dried to obtain white solid-**6a**, **6b**.

Biological Assay

All the title compounds were tested at organism reared in the laboratory and the tested insects were cultured in accordance with the literature.[41] The bioassay was replicated at 25 ±1 °C according to statistical requirements. Assessments were made on a dead/alive basis and mortality rates were corrected by applying Abbott's formula.[42] Evaluation standard was based on a percentage scale of 0-100, in which 0 has no activity and 100 equals total kill.

Larvicidal activity against oriental armyworm

The insecticidal activity of compounds **8a–8n** and Chlorantraniliprole against oriental armyworm was conducted according to the leaf-dip method by referring to the reported method.[43] The summarized larvicidal activity was shown in Table 1.

Larvicidal activity against diamondback moth

The insecticidal activity of compounds **8a**-**8n** and Chlotantraniliprole was tested by the leaf-dip method according to the reported method.[44] The larvicidal activity was summarized in Table 2.

Calcium Imaging

The mechanism of title compounds was investigated referring to the previous articles.[45] Fluorescence values were expressed as F/F_0, where F_0 meant the resting (or baseline) fluorescence and represented the change in fluorescence after the application of drug.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

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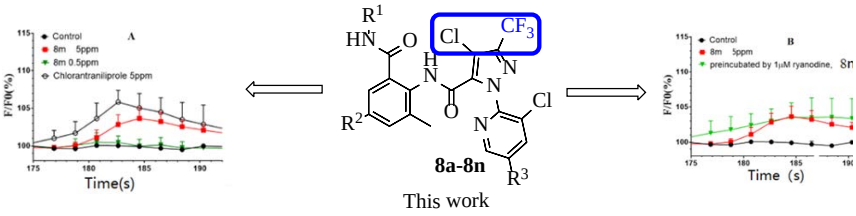

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For diamondback moth, **8m** exhibited better activity than Chlorantraniliprole at a hundred fold preference. The calcium imaging technique experiment results suggested that compound **8m** could increase the intracellular $[Ca^{2+}]_i$ and further experiments confirmed that the target of this series of compounds could be RyRs in the central larvae neurons of oriental armyworm.