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Original article

Design, synthesis and insecticidal activity of novel anthranilic diamides with benzyl sulfide scaffold

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ABSTRACT

A series of novel anthranilic diamides with benzyl sulfide scaffold were synthesized, in which *N*-pyridylpyrazole moiety generally regarded as key pharmacophore was abandoned. The target compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. The preliminary bioassays indicated that half of the title compounds were endowed with good insecticidal activities against armyworm (*Mythimna sepatara*) at the concentration of 500 mg/L. Exhilaratingly, the synthesized compound **3a** was also active against *Tetranychus cinnabarinus* at 100 mg/L. The difference in activities between the target compounds was influenced by the substituents, which provided some hints for further investigation on structure modifications.

1. Introduction

The current status of insecticide resistance and the underlying resistance in target species is a serious problem in plant protection [1]. Therefore, the exploration of novel insecticides with new mode of action has attracted much interest. In the past decade, the newest major class of insecticides, the diamides, inaugurated the new era of insecticides. Chlorantraniliprole [2] and flubendiamide [3] (Fig. 1), sharing a unique mode of action on the insect ryanodine receptors with high potency and remarkable selectivity, have been rocketed into a position of great status in agrochemicals.

Anthranilic diamides, which acting on insect ryanodine receptors (RyRs), are fasting growing class insecticides in modern crop protection for their highly potent activity, low ecotoxicity and broad insecticidal spectra [4]. According to the modified structures of anthranilic diamides described in a sizable number of patents and papers in recent years, the common molecular structural features of anthranilic diamides can be categorized into three parts (Fig. 2): the *N*-pyridylpyrazole moiety (a) [5–8], the anthraniloyl moiety (b) [9–13] and aliphatic amide moiety (c) [14–17]. A major emphasis on researching for novel anthranilic diamides involved the modifications related to part (b) and (c). In previous studies, it was found that replacing the *N*-pyridylpyrazole moiety with 1, 2, 3-thiadiazole or trizolopyrimidine ones [18,19], the anthranilic diamides analogs showed no insecticidal activities. On the basis of above observations, it was reasoned that the pyrazole heterocycle in the *N*-pyridylpyrazole moiety (a) is a key pharmacophore in this kind of compounds. Therefore, altering the *N*-pyridylpyrazole moiety (a) by other substituents on the structural modifications was seldom reported.

Element sulfur is undoubtedly linked to the pesticides in the history of crop protection. Sulfide scaffold is a highly efficient pharmacophore in the molecular design. The introduction of sulfide scaffold contributed to higher activities and was responsible for low mammalian toxicity [20]. In recent years, the sulfide scaffold is widely used in several commercialized insecticides, for example, flubendiamide [3], thiacloprid [21] and sulfoxaflor [22] (Fig. 3). Then, the program of incorporation of benzyl sulfide scaffold into the anthraniloyl moiety (b) was initiated in this study. Enlightened by all of intriguing reasons above, we herein designed and synthesized a series of novel anthranilic diamides bearing benzyl sulfide scaffold (Fig. 4).

2. Experimental

2.1. Experiments

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Melting points (mp) were recorded on Büchi B540 apparatus and are uncorrected. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 (400 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 spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055

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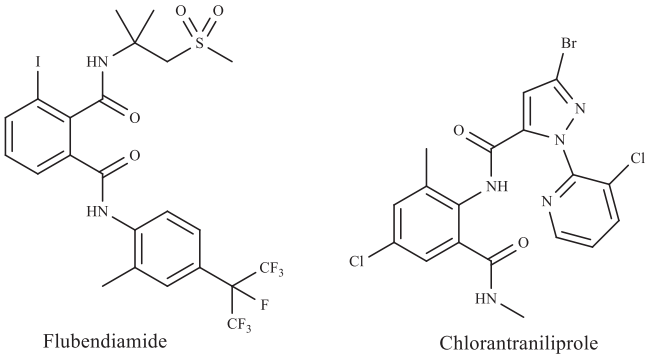


Fig. 1. Commercialized diamide insecticides.

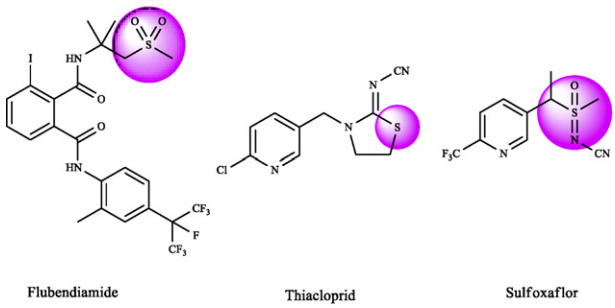


Fig. 3. Commercialized insecticides with sulfides.

instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light.

*Preparation of 2-amino-6-bromo-N-(3-bromo-2-(methylcarbamoyl)phenyl)benzamide (**1**):* A mixture of 2-amino-6-bromobenzoic acid (1.0 mmol), methylamine water solution (1.5 mmol), EDCI (2.0 mmol), HOBt (0.2 mmol) in DCM was stirred at room temperature and monitored by TLC. After completion, the mixture was diluted with DCM, washed with water twice, dried over anhydrous Na_2SO_4, evaporated, and chromatographed (ethyl acetate - petroleum ether) to afford the compound **1**.

*Preparation of 2-amino-N-(3-(benzylthio)-2-(methylcarbamoyl)-phenyl)-6-bromobenzamide (**2**):* A mixture of **1** (1.0 mmol), thiobenzyl alcohol (1.2 mmol), K_2CO_3 (1.2 mmol) in DMF was stirred at room temperature for 12 h. After completion, the mixture was removed under reduced pressure and taken into DCM, followed by extraction with water and brine. The organic phase was then dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford the crude product, which, upon further purification by column chromatography (ethyl acetate-petroleum ether), afforded intermediate **2**.

*General synthetic procedure for the title compound **3a–w***: A mixture of various carboxylic acids (1.0 mmol), an excess of thionyl chrolide (5 mL) was refluxed for 2 h and concentrated *in vacuo* to give corresponding acyl chloride (quant). The corresponding acyl chloride was dissolved in 2 mL anhydrous DCM, then added dropwise to a solution of compound **2** (1.0 mmol), DIPEA (1.2 mmol) in 15 mL anhydrous DCM in an ice bath. The reaction was then stirred at room temperature and monitored by TLC, after completion, the solvent was evaporated under reduced pressure. The residual solid was purified by column chromatography on silica gel with ethyl acetate - petroleum ether as eluent to afford the title compound **3a**–**w**.

*Preparation of N-(2-((3-(benzylsulfinyl)-2-(methylcarbamoyl)phenyl)carbamoyl)-3-bromophenyl)-2-bromo-3-nitrobenzamide (**4a**):* To a solution of the title compound **3b** (1.0 mmol) in 10 mL DCM was added *m*-chloroperoxy benzoic acid (MCPBA) (1.05 mmol). The reaction was carried out at room temperature, and the progress of the reaction was monitored by TLC. After completion, the mixture was poured into water, and then extracted with DCM. The organic layer was washed with aqueous sodium hydrosulfite and an aqueous sodium carbonate solution respectively, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with ethyl acetate–petroleum ether as eluent to afford the title compound **4a**.

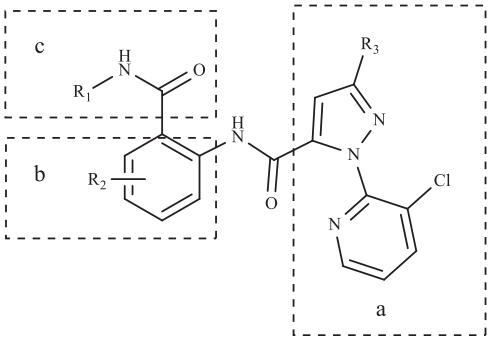


Fig. 2. The chemical structure of anthranilic diamides.

2.2. Biological assay

All bioassays were performed on representative test organisms reared 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 two concentrations of 500.0 mg/L and 100.0 mg/L. For comparative purposes, avermectins as control was tested under the same conditions.

Insecticidal test for armyworm (Mythimna sepatara): The activities of the designed compounds against armyworm were tested using previously reported procedures [23]. The insecticidal activity against armyworm was tested by foliar application. Individual corn (*Zea mays*) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the compounds solution and exposed to dry. The dishes were infested with 10 third-instar larvae and 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 subjected to probit analysis as before.

Insecticidal test for Tetranychus cinnabarinus: The activities of the new compounds against *T. cinnabarinus* were assessed according to the reported procedure [24]. Cut round sections from chemically untreated broad bean leaves. Leaves must be in good condition. Collect about 40 adult mites with the fine pointed brush onto each

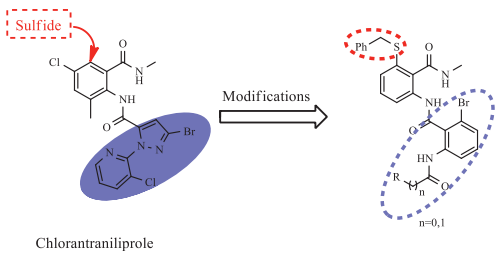
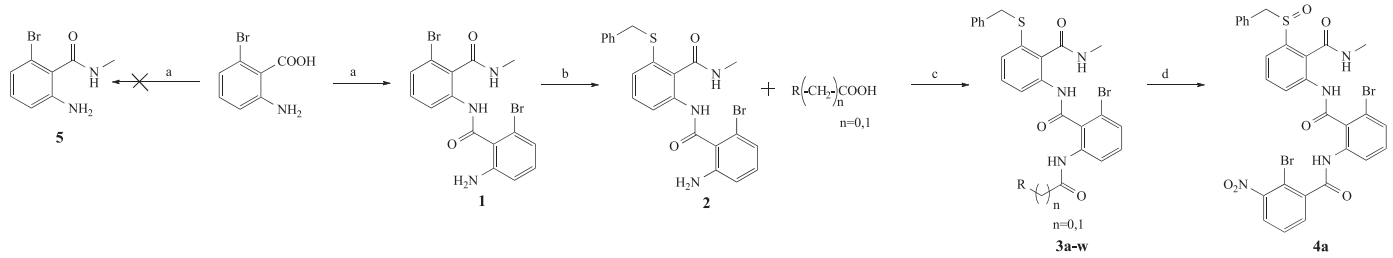


Fig. 4. Design of novel anthranilic diamides with benzyl sulfide.



Scheme 1. Reagents and conditions: (a) methylamine water solution (25.0 %–30.0 %), EDCI, HOBt, DCM, r.t.; (b) thiobenzyl alcohol, K_2CO_3, DMF, r.t.; (c) (i) $SOCl_2$, reflux; (ii) DIPEA, DCM, r.t.; (d) MCPBA, DCM, r.t.

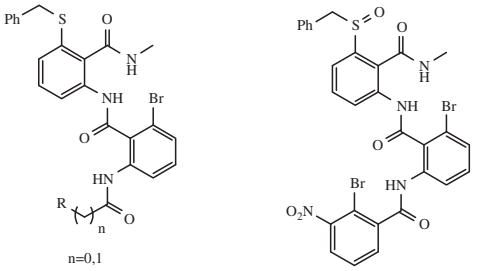
leaf section. The leaf disk with mites placed under the Potter spray tower, and then sprayed with test liquids (pressure 5 lb/in^2). The test set with the highest concentrations of organic solvents Tween water as a blank control. The leaf discs with mite are air dried and placed at a room with temperature of 24–26 °C, photoperiod 14 h. Using hand lens assess mortality after 96 h by checking each mite's ability to show movement in response to a touch with a small brush. Express results as percentage mortality and correct for untreated mortality using Abbott's formula. Each process was repeated for 3 times.

3. Results and discussion

3.1. Synthesis

The synthetic route of the title compounds was depicted in Scheme 1. The target compounds **3a**–**w** were synthesized by a three-step procedure. In the first step, the treatment of 2-amino-6-bromobenzoic acid with methylamine water solution in the presence of EDCI and HOBt afforded compound **1** rather than compound **5** in good yields, which was confirmed by ^{1}H NMR. We

Table 1
Insecticidal activities of compounds **3a**–**w** and **4a** against armyworm (*M. sepatara*) and *T. cinnabarinus*.



Compd.	*R*	*n*	Conc. (mg/L)	Mortality (%)	
				M. sepatara	*T. cinnabarinus*
3a	4-Cyano-3-fluorophenyl	0	500	100	100
			100	0	60
3b	2-Bromo-3-nitrophenyl	0	500	100	90
3c	2,5-Dimethoxyphenyl	0	500	100	80
3d	4-Chlorophenyl	0	500	100	0
3e	4-Bromo-2,3-difluorophenyl	0	500	100	0
3f	6-Fluoropyridin	0	500	90	0
3g	2-Trifluoromethoxyphenyl	0	500	80	0
3h	Styrene	0	500	60	0
3i	3-Bromo-5-trifluoromethoxyphenyl	0	500	50	0
3j	2-Bromo-4,5-difluorophenyl	0	500	0	100
			100	0	10
3k	4-Trifluoromethylphenyl	0	500	0	90
3l	2,4,5-Trifluoro-3-methoxyphenyl	0	500	0	80
3m	2-Bromo-6-fluorophenyl	0	500	0	80
3n	6-Trifluoromethylpyridin	0	500	0	0
3o	Methyl	0	500	0	0
3p	2-Iodophenyl	0	500	0	0
3q	2-Fluoro-5-iodophenyl	0	500	0	0
3r	2,3,4,5,6-Pentafluorophenyl	0	500	0	0
3s	2-Bromo-4-trifluoromethylphenyl	1	500	0	90
			100	0	10
3t	2,4,6-Trifluorophenyl	1	500	0	0
3u	4-Nitrophenyl	1	500	90	0
3v	4-Methoxyphenyl	1	500	90	0
3w	Naphthalene	1	500	90	0
4a	–	0	500	0	0
Avermectins	–		500	100	100
ns			100	100	100

proposed that compound **1** was prepared *via* self-condensation of 2-amino-6-bromobenzoic acid, and then coupled with methylamine. With the key intermediate **1** in hand, conversion of **1**–**2** was then carried out with thiobenzyl alcohol in the DMF using K_2CO_3 as acid acceptor. Fortunately, owing to the electronic effect of aromatic substitutes, the amino group deactivated the bromo group in the same aromatic ring, so that compound **2** was the major product with the yield of 65%, which was further convinced by comparing ^{1}H NMR data of compound **1** and **2** (see Supporting information). Various carboxylic acids were treated with thionyl chrolide and then coupled with intermediate **2** in the presence of DIPEA to provide the title compounds of amide **3a**–**w** in moderate to good yields. By oxidation of the compound **3b** with MCPBA, compound **4a** could be easily prepared in high yields.

3.2. Insecticidal activities

To evaluate the overall insecticidal activities of anthranilic diamides with benzyl sulfide, two representative insects from two different orders (Lepidoptera and Acarina) were selected as the target pest. The testing results against two insects were listed in Table 1. For comparative purposes, avermectins as control was also tested under the same conditions.

Insecticidal test for armyworm (M. sepatara): The larvicidal activity against armyworm was summarized in Table 1. The title compounds **3a**–**3e** exhibited 100% mortality against armyworm at 500 mg/L; the other compounds **3f**–**3i** and **3u**–**3w** showed moderate to high activities, and had 50 %–90 % mortality at 500 mg/L. This suggested that activities varied significantly depending on the types and patterns of the substituents. When *R* was substituted by F, Cl, Br, OCF_3, OCH_3, CN and NO_2 in the benzene ring and heterocycle, most of compounds showed activities except for introduction of CF_3 and I group. Replacement of substituents in the benzene ring with acetyl unit, compound **3o** was inactive against armyworm. Unexpectedly, the oxidated compound **4a** originated from **3b** lost the activities against armyworm, which gave us some hints to stop further modifications on the sulfur into the sulfoxide. The results showed that most of the title compounds without the *N*-pyridylpyrazole moiety still exhibited insecticidal activities against armyworm, which implied a new molecular design to obtain active compounds against armyworm.

Insecticidal test for T. cinnabarinus: The title compounds **3a, 3b, 3c, 3j, 3k, 3l, 3m** and **3t** displayed excellent insecticidal activities against *T. cinnabarinus* (Table 1) and had >80% mortality at the concentration of 500 mg/L. Moreover, when the test concentration was lowered to 100 mg/L, the activity of compound **3a, 3j** and **3s** was 60%, 10% and 10%, respectively. It was concluded that the substituted benzene ring was favorable for activities compared with heterocycle and acetyl unit. The bioassay results suggested that some of the target compounds with benzyl sulfide scaffold showed the insecticidal potency against *T. cinnabarinus*. To best of our knowledge, the spectra were extended compared with anthranilic diamides analogs.

4. Conclusion

In conclusion, a series of novel anthranilic diamides derivatives, which altered *N*-pyridylpyrazole moiety and endowed with benzyl sulfide scaffold, were designed and synthesized in this study. The insecticidal activities of the title compounds against armyworm (*M. sepatara*) at 500 mg/L were evaluated; activities were significantly influenced by the substituents. In particular, the preliminary bioassays indicated that one-third of the synthesized compounds exhibited excellent insecticidal activities against *T. cinnabarinus*, which showed some differences in activities compared with anthranilic diamides analogs. Further studies on the structural optimizations and the special activities of the title compounds are in progress.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.04.047.

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