Received: 30 November 2020 | Revised: 16 February 2021 | Accepted: 26 March 2021

DOI: 10.1002/jhet.4268

ARTICLE

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Design, synthesis, and insecticidal activities of novel diamide derivatives with alpha-amino acid subunits

Rui-Jia Chen[1] | **Jun-Jie Wang**[1] | **Li Han**[1] | **Yu-Cheng Gu**[2] | **Zhi-Ping Xu**[1] | **Jia-Gao Cheng**[1] | **Xu-Sheng Shao**[1] | **Xiao-Yong Xu**[1] | **Zhong Li**[1,3]

[1]Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai, China

[2]Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, UK

[3]Shanghai Collaborative Innovation Center for Biomanufacturing Technology, East China University of Science and Technology, Shanghai, China

Correspondence
Zhong Li, Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, 200237 Shanghai, China.
Email: lizhong@ecust.edu.cn

Funding information
Innovation Program of Shanghai Municipal Education Commission, Grant/Award Number: 2017-01-07-00-02-E00037; National Key Research and Development Program of China, Grant/Award Number: 2017YFD0200500; Syngenta PhD Fellowship Award

Abstract

A series of diamide derivatives containing α-amino acids were designed and synthesized. These compounds were evaluated for their insecticidal activities against *Plutella xylostella*, *Mythimna separate*, *Myzus persicae*, and *Tetranychus cinnabarinus*. Most of the title compounds containing an L-phenylglycine skeleton were endowed with good activities at the concentration of 500 mg·L^{-1}. Compounds (**R)-A6** showed a potential value for further optimization as an insecticidal lead with the LC_{50} value of 86.8 mg·L^{-1}.

1 | INTRODUCTION

Diamide insecticides (Figure 1), represented by flubendiamide (phthalic) and chlorantraniliprole (anthranilic), are classified as the group 28 insecticides with unique mechanism of action in Insecticide Resistance Action Committee Mode of Action Classification Scheme due to their particular structures and action mechanisms. Diamide insecticides act selectively on insect ryanodine receptors (RyRs) which control the calcium channel [1]. They can cause an uncontrolled release of calcium ions and the ultimate death of pests [2–5]. Since diamide insecticides exhibit good activities against lepidopteran pests, less toxicity to mammals, and no cross-resistance with other existing insecticides, they are wildly applied in integrated pest management programs [6,7]. However, a series of problems arose in the field such as high persistence in soil, chronic risk to aquatic invertebrates [8,9], and increased resistance [10–12] of pests. Structural modifications of diamide insecticides have attracted the continuous attention of researchers.

The chemical structures of anthranilic insecticides can be generally divided into two amide linkers and three components: terminal aliphatic moiety (Part A), central

This paper is dedicated to Professor Youyou Tu, the 2015 Nobel Prize Laureate of Physiology or Medicine on the occasion of her 90th birthday.

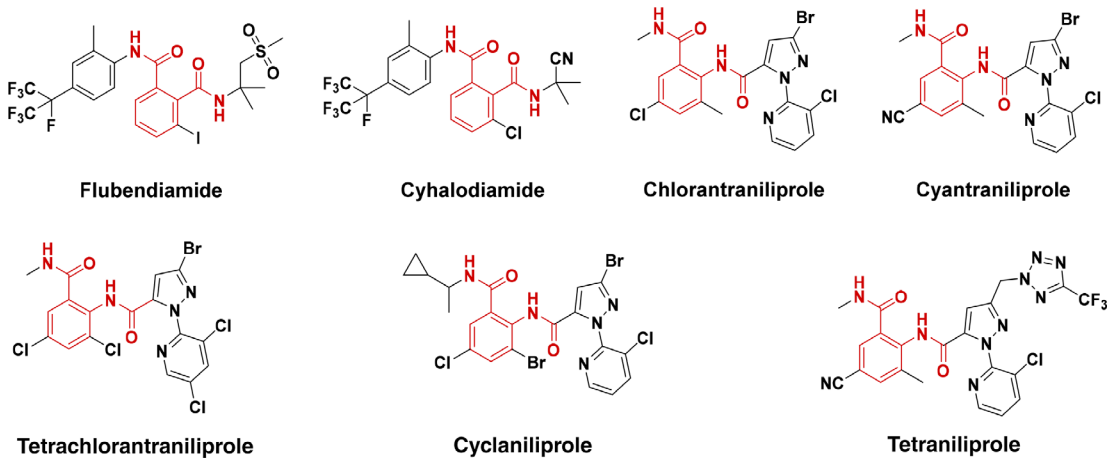


FIGURE 1 Commercialized diamide insecticides

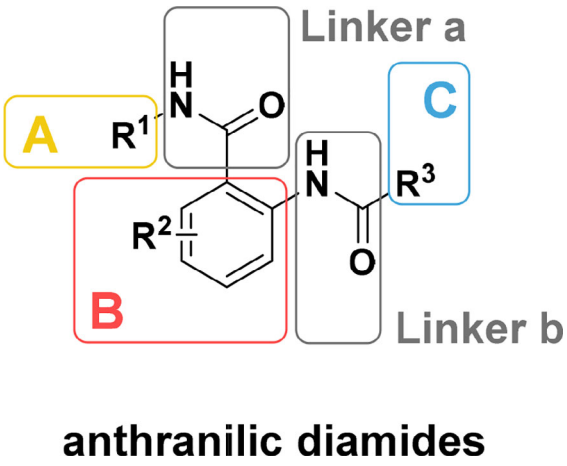


FIGURE 2 General structure of diamide insecticides

aromatic moiety (Part B), and terminal heterocyclic moiety (Part C) (Figure 2). In recent years, quantities of researches have been reported for modification on anthranilic insecticides. But most of them were devoted in Part A [13,14], Part C [15–17], or amide linkers [18].

The coexistence of amino (—NH_2) groups, carboxyl (—COOH) groups, and various side chains contributes to the attractive properties of amino acids and their corresponding derivatives. And α-amino acids, whose amino and carboxyl groups attached to the same (α-) carbon atom, have particular importance in biology, pharmacology, and chemistry [19,20]. Twenty-two α-amino acids, as the building blocks of proteins, perform extensive functions including forming the scaffolding system of cells, catalyzing biochemical reactions, and transporting various molecules. Some α-amino acids, represented by glutamate, glycine, and cysteine, provide the neurotransmitters for vertebrates. And α-amino acids are the precursors of vast biomolecules such as porphyrins, purines, and pyrimidines. Exemplified by insulin and bacitracin, amino acids have their lion's share in the early discoveries of the modern drug. Due to the ease of synthesizing amino acids with different side chains, the convenience of further structural modification, the desire of "escape from flatland" and the diversity of steric structure and pharmacologic properties, amino acids are valuable as diverse elements for potential central components, peptidomimetic drugs, and structure–activity relationship (SAR) investigations in drug discoveries [21–25]. For decades, α-amino acid fragments have appeared in more drugs, such as Nateglinide [26], Telaprevir [27], Pasireotide [28], and Pramiracetam [29], while they are found only in a small number of agrochemicals [30,31] (Figure 3).

The distance between pharmacophoric groups can affect the activity of compounds. The two amide bonds of flubendiamide and chlorantraniliprole are both situated at ortho-positions. Broflanilide, a commercialized insecticide, has similar terminal groups to the phthalic and anthranilic insecticide [32]. The diamide structure of broflanilide is not ortho-position but meta-position while broflanilide acts on the insect γ-aminobutyric acid receptors instead of RyRs [33,34]. In the studies of structural modifications on diamide insecticides, some compounds with different distances between the two amide bonds also exhibited insecticidal activities against lepidopteran pests [35–37].

In our previous research, we have modified the phthalic or anthranilic central subunits (Part B) of existing diamide insecticides. And several series of novel diamide compounds with different distances between two amide bonds and different biological activities were reported [38–40]. Encouraged by those discoveries, we tried to expand our scope of the investigation to other acceptable central components of diamide insecticides.

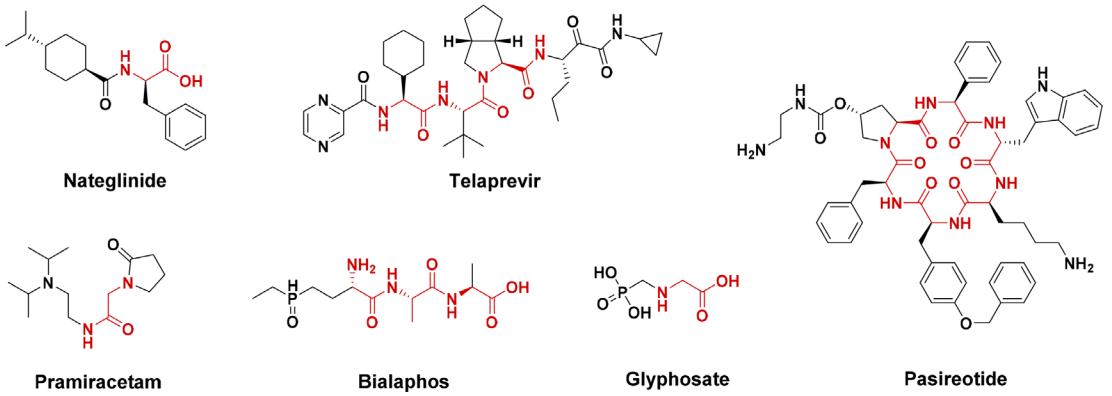


FIGURE 3 Commercialized drugs and agrochemicals with amino acid skeletons

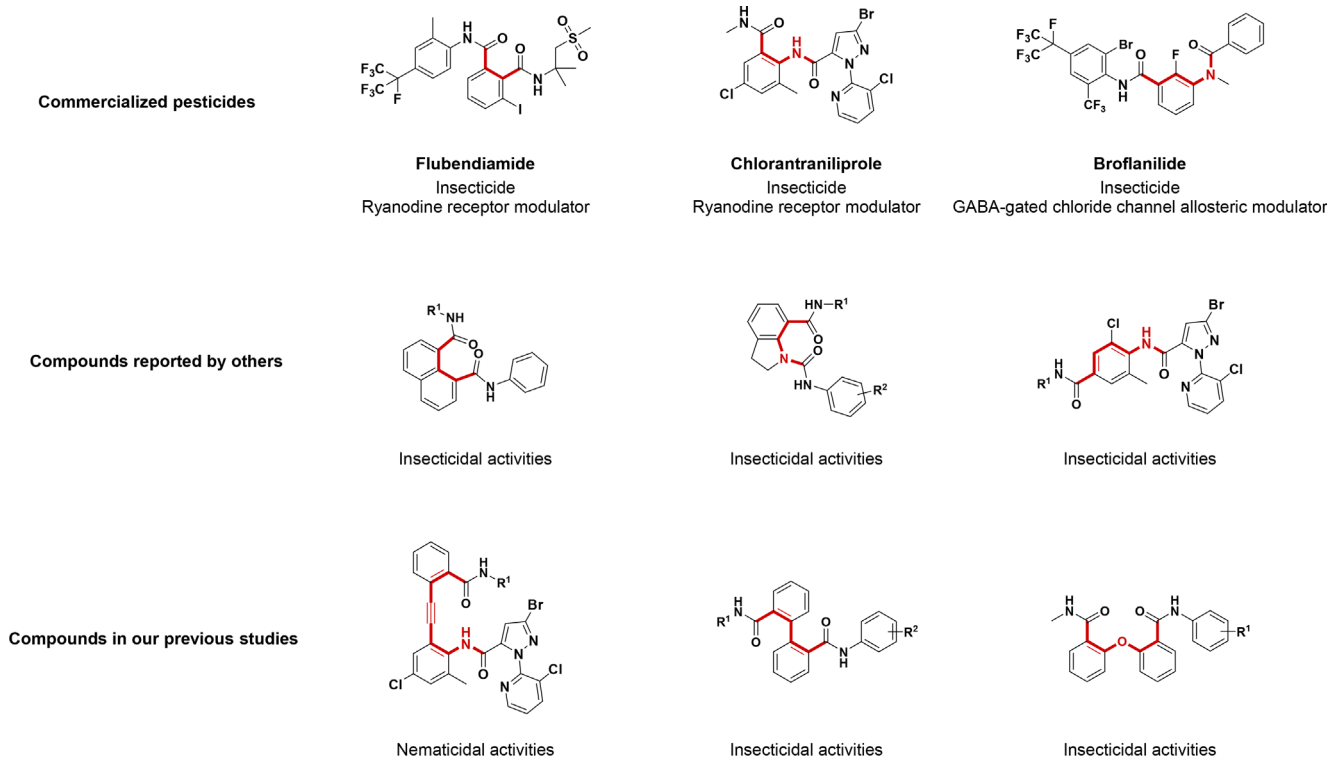
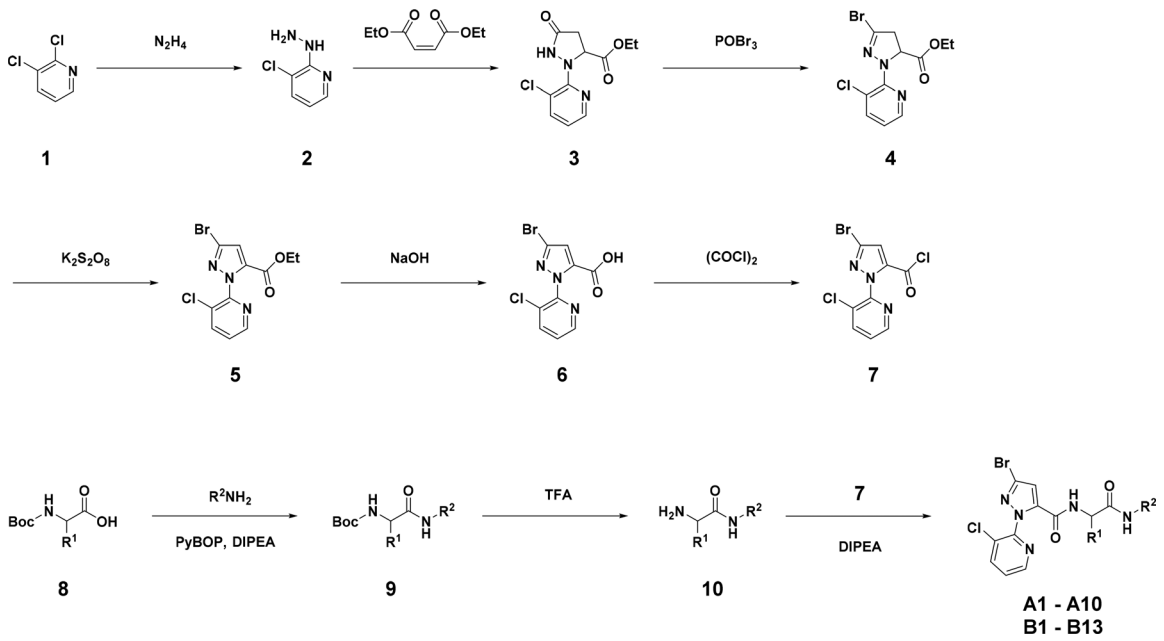


FIGURE 4 Molecular design of novel α-diamides

In this study, α-amino acids were introduced to replace the original central component of chlorantraniliprole. A series of novel diamides with two amide bonds linked to the same carbon atom were designed, synthesized, and evaluated for their insecticidal activities. Figure 4 shows the molecular design strategy for the target compounds.



SCHEME 1 General synthetic procedure for target compounds **A1–A10 and B1–B11**

2 | MATERIAL AND METHODS

2.1 | Instrumentation and chemicals

Unless otherwise noted, all reagents and solvents were obtained from commercial sources and used without further purification. Melting points (m.p.) were recorded on Büchi Melting Point B-540 (Büchi Labortechnik AG, Flawil, Switzerland) are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 spectrometer with dimethyl sulfoxide (DMSO)-d_6 or $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in δ (parts per million). High-resolution electron mass spectra were performed on a micromass liquid chromatography time-of-flight spectrometer. Specific rotations were recorded on Polarimeter (Rudolph Research Analytical Autopol III). Analytical thin-layer chromatography was performed on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet light.

2.2 | Insecticidal assay

According to statistical requirements, the bioassay was repeated three times at 25 ± 1°C. All compounds were dissolved in DMSO and diluted with water containing Triton X-100 (0.1 mg·L^{-1}) to obtain series concentrations of 500.0, 100.0 mg·L^{-1}, and others for bioassays.

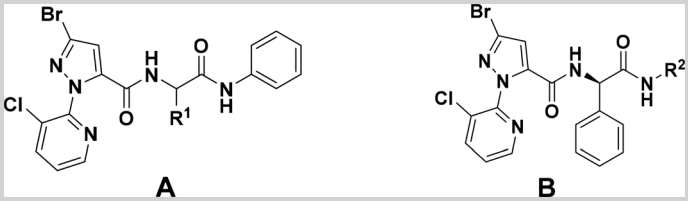
3 | RESULT AND DISCUSSION

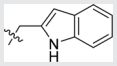
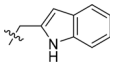
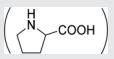
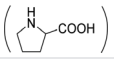
3.1 | Synthesis

As illustrated in Scheme 1, the target compounds **A1–A10** and **B1–B11** were obtained through a four-step reaction from the key intermediate 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid **6** and corresponding *tert*-butoxycarbonyl amino acids **8**. Based on the similar method reported in the related literature [41], **6** was synthesized from commercially available 2,3-dichloropyridine **1** with minor modifications. Compound **1** and hydrazine hydrate (50% in water) were directly refluxed without other solvents to obtain 3-chloro-2-hydrazinylpyridine **2** in 83% yield. Compound **3** was prepared by the condensation of **2** and diethyl maleate in the presence of sodium ethoxide (NaOEt). Treat **3** with phosphorus oxybromide ($POBr_3$) in acetonitrile (MeCN) to get the bromine-substituted pyrazoline **4** in 95% yield. Subsequent oxidation of **4** by potassium persulfate afforded the *N*-pyridylpyrazole **5**. And the intermediate acid **6** was obtained from the hydrolysis of ester **5** in quantitative yield.

In the present of benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBop) and *N*,*N*-diisopropylethylamine (DIPEA), amides **9** could be conveniently prepared in 67%–92% yield by the reaction of commercially available Boc-protected amino acids **8** and various amines including aliphatic amines and substituted anilines. Deprotected by trifluoroacetic acid,

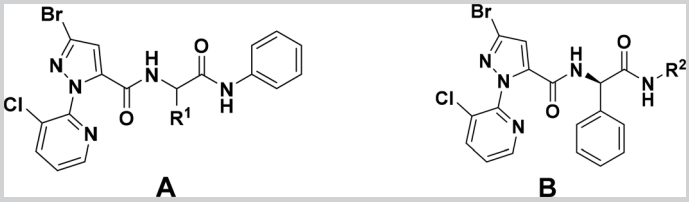
TABLE 1 Insecticidal activities of compounds **A1–A10** and **B1–B11**



Compound	R^1	R^2	Conc. ($mg \cdot L^{-1}$)	Mortality (%) *Plutella xylostella* 72 h	*Mythimna separate* 72 h	*Myzus persicae* 48 h	*Tetranychus cinnabarinus* 72 h
(S)-A1		Ph	500	0	0	0	0
(R)-A1		Ph	500	50.0	31.0	0	0
(S)-A2	$-CH(CH_3)_2$	Ph	500	0	75.7	0	0
(R)-A2	$-CH(CH_3)_2$	Ph	500	0	17.0	0	0
(S)-A3		Ph	500	60.0	88.0	0	0
(R)-A3		Ph	500	46.7	73.3	0	0
(S)-A4		Ph	500	50.0	13.0	0	0
(R)-A4		Ph	500	0	11.0	0	0
(S)-A5		Ph	500	76.7	70.0	0	0
(R)-A5		Ph	500	80	56.7	0	0
(S)-A6	Ph	Ph	500	96.7	80.0	0	0
(R)-A6	Ph	Ph	500	100	100	0	0
			100		60	0	0
(S)-A7	Benzyl	Ph	500	11.2	23.6	0	0
(R)-A7	Benzyl	Ph	500	0	0	0	0
(S)-A8		Ph	500	90	63.3	0	0
(R)-A8		Ph	500	83.3	13.3	0	0
(S)-A9	Isobutyl	Ph	500	0	14.3	0	0
(R)-A9	Isobutyl	Ph	500	0	16.6	0	0
(S)-A10	Methyl	Ph	500	21.6	33.3	0	0
(R)-A10	Methyl	Ph	500	33.3	51.6	0	0
(R)-B1	Ph	Cyclopropyl	500		0		
(R)-B2	Ph	Cyclopentyl	500		0		
(R)-B3	Ph	Isopropyl	500		0		
(R)-B4	Ph	Propyl	500		0		
(R)-B5	Ph	Isobutyl	500		100		
			100		58.3		
(R)-B6	Ph	4- Cl-phenyl	500		100		
			100		34.1		
(R)-B7	Ph	4-CN-phenyl	500		11.6		
			100		0		

(Continues)

TABLE 1 (Continued)



(R)-B8	Ph	2-CH_3-phenyl	500		100		
			100		0		
(R)-B9	Ph	3-CH_3-phenyl	500		100		
			100		37.2		
(R)-B10	Ph	4-CH_3-phenyl	500		100		
			100		18.7		
(R)-B11	Ph	4-OCH_3-phenyl	500		0		
			100		0		
CK				0	0	0	0
Chlorantraniliprole			10	100	100		
Imidacloprid			10			100	
Avermectin			10				100

9 was converted to the corresponding amines **10**. Meanwhile, **6** was prepared into acid chloride **7** with oxalyl chloride [$(COCl)_2$] and then coupled with **10** using DIPEA as acid capture to obtain target compounds **A1**–**A10** and **B1**–**B10** in 72%–85% yield. The structures of those compounds were confirmed by analyzing their NMR and ESI spectral data.

3.2 | Insecticidal activity

The insecticidal activities of α-diamide derivatives against *Plutella xylostella*, *Mythimna separate*, *Myzus persicae*, and *Tetranychus cinnabarinus* were evaluated, using chlorantraniliprole as the control compound. The results are listed in Table 1.

At the outset of the study, we use aniline as the fixed substituent of Part A and prepared 20 derivatives **A1**–**A10** with differing side chains to investigate the effects on biological activities of replacing the central components with α-amino acids. The results indicated that most of the compounds exhibited moderate larvicidal activities against *P. xylostella* and *M. separate* at the concentration of 500 $mg{\cdot}L^{-1}$ (Table 1).

The side chains and configurations of central amino acids are what the insecticidal activities of title compounds depended on, as the two factors often determine the difference in the biological activities of drugs containing amino acid subunits [42,43]. At the concentration of 500 $mg{\cdot}L^{-1}$, **(S)-A1** containing (S)-tryptophan had no insecticidal activities on *P. xylostella*, and **(R)-A1** containing (R)-tryptophan showed moderate activities. At the same concentration, there was a 60% difference in the lethality rate against *M. separate* between the enantiomers **(S)-A2** and **(R)-A2** while the difference between **(S)-A3** and **(R)-A3** was about 15%. **(S)-A4** and **(R)-A4** contained methionines with a different configuration. These two compounds showed similar insecticidal activities against *M. separate* but their insecticidal activities on *P. xylostella* were different. As the insecticidal activities of **(S)-A3**, **(S)-A6**, and **(R)-A6** against *M. separate* and the activities of **(R)-A5**, **(S)-A6**, **(R)-A6**, **(S)-A8**, and **(R)-A8** against *P. xylostella* are all over 80% at the concentration of 500 $mg{\cdot}L^{-1}$, *β*-methyl (S)-aspartate, (R)-proline, phenylglycines, and *O*-methyl-serines were proved to be acceptable α-amino acid central components for diamide insecticides. Among all title compounds, the activities of **(R)-A6** were relatively higher than that of others with the LC_{50} value of 86.8 $mg{\cdot}L^{-1}$ against *M. separate*. The larvae treated by **(R)-A6** ceased feeding, sequentially contracted, and ultimately died. The abnormal symptoms were similar to those caused by chlorantraniliprole. It indicated that **(R)-A6** might exhibit its activity by activating insect RyRs.

We took compound **(R)-A6** as the potent lead for further optimization on Part A. Various amino groups, including aliphatic amines and substituted anilines, were

investigated and 11 compounds **B1**–**B11** were prepared. Majority of the compounds in this subseries exhibited good larvicidal activities against *M. separate*, but they did not lead to significant improvement over the lead.

Aliphatic amine groups except isobutyl [compound **(R)-B5**] eliminated the insecticidal activity. It indicated that the introduction of a big steric amino group in Part A has a positive effect on the activities against *M. separate*, contrary to the conclusion in the discovery of chlorantraniliprole. And depending on the types of substituents at the 4-position of aniline, the insecticidal activities varied. Addition of a strong electron-withdrawing [—CN, compound **(R)-B7**] or electron-donating [—OCH_3, compound **(R)-B11**] groups to the para position of aniline reduced the activities. And the compounds substituted with a chlorine atom [compound **(R)-B6**] or methyl [compound **(R)-B10**] at the 4-position showed similar activities to **(R)-A6**. Meanwhile, diversity at different positions of aniline [compound **(R)-B8**, **(R)-B9**, and **(R)-B10**] and the corresponding changes on insecticidal activity were investigated. The activity against *M. separate* of **(R)-B9** with methyl substituted at 3-position was best among the three compounds and slighter lower than that of **(R)-A6**. The original **(R)-A6** was still the most satisfactory one in our series.

In this study, the original central anthranilic subunit (Part B) of chlorantraniliprole was replaced by α-amino acids and a series of novel diamide derivatives were designed and synthesized. The preliminary bioassays showed that compounds possessing L-phenylglycine skeleton exhibited good insecticidal activities against *M. separate*, and **(R)-A6** had the LC_{50} value of 86.8 $mg{\cdot}L^{-1}$. It indicated that the derivatives with L-phenylglycine as the central component can be a lead for the discovery of novel insecticides. Further study on the diamides with amino acid subunits is ongoing in our laboratory.

ACKNOWLEDGMENTS

This work was financial supported by National Key Research and Development Program of China (2017YFD0200500) and Innovation Program of Shanghai Municipal Education Commission (2017-01-07-00-02-E00037), and Syngenta PhD Fellowship Award to Ruijia Chen.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Data S1 of this article.

ORCID

Rui-Jia Chen https://orcid.org/0000-0001-7614-7576
Yu-Cheng Gu https://orcid.org/0000-0002-6400-6167

REFERENCES

[1] IRAC, http://www.irac-online.org/content/uploads/MoA-classification.pdf (accessed April 2020).
[2] J. R. Bloomquist, *Annu. Rev. Entomol.* **1996**, *41*, 163.
[3] G. P. Lahm, T. P. Selby, J. H. Freudenberger, T. M. Stevenson, B. J. Myers, G. Seburyamo, B. K. Smith, L. Flexner, C. E. Clark, D. Cordova, *Bioorg. Med. Chem. Lett.* **2005**, *15*(22), 4898.
[4] M. Tohnishi, T. Nishimatsu, K. Motoba, T. Hiroola, A. Seo, *J. Pestic. Sci.* **2010**, *35*(4), 508.
[5] G. P. Lahm, T. M. Stevenson, T. P. Selby, J. H. Freudenberger, D. Cordova, L. Flexner, C. A. Bellin, C. M. Dubas, B. K. Smith, K. A. Hughes, J. G. Hollingshaus, C. E. Clark, E. A. Benner, *Bioorg. Med. Chem. Lett.* **2007**, *17*(22), 6274.
[6] K. E. Brugger, P. G. Cole, I. C. Newman, N. Parker, B. Scholz, P. Suvagia, G. Walker, T. G. Hammond, *Pest Manage. Sci.* **2010**, *66*(10), 1075.
[7] A. M. Koppenhöfer, E. M. Fuzy, *Biol Control* **2008**, *45*(1), 93.
[8] B. E. Erickson, *Chem. Eng. News* **2016**, *94*(10), 18.
[9] European Food Safety Authority, *EFSA J* **2015**, *13*(11), 4308.
[10] X. Wang, Y. Wu, *J. Econ. Entomol.* **2012**, *105*(3), 1019.
[11] X. Wang, S. K. Khakame, C. Ye, Y. Yang, Y. Wu, *Pest Manage. Sci.* **2013**, *69*(5), 661.
[12] L. M. S. Ribeiro, V. Wanderley-Teixeira, H. N. Ferreira, A. A. C. Teixeira, H. A. A. Siqueira, *Bull. Entomol. Res.* **2014**, *104*(1), 88.
[13] J. Andre, O. A. Cornelius, *WO 2006032462*, **2006**.
[14] Y. Xie, S. Zhou, Y. Li, S. Zhou, M. Chen, B. Wang, L. Xiong, N. Yang, Z. Li, *Chin. J. Chem.* **2018**, *36*(2), 129.
[15] X. Zhang, Y. Li, J. Ma, H. Zhu, B. Wang, M. Mao, L. Xiong, Y. Li, Z. Li, *Bioorg. Med. Chem.* **2014**, *22*(1), 186.
[16] Z. Huang, J. Tong, S. Zhou, L. Xiong, H. Wang, Y. Zhao, *J. Heterocycl Chem.* **2015**, *53*(4), 1036.
[17] C. Wu, X. Yu, B. Wang, J. Liu, F. Meng, Y. Zhao, L. Xiong, N. Yang, Y. Li, Z. Li, *J. Agric. Food Chem.* **2020**, *68*(35), 9319.
[18] J. Zhang, J. Xu, B. Wang, Y. Li, L. Xiong, Y. Li, Y. Ma, Z. Li, *J. Agric. Food Chem.* **2012**, *60*(31), 7565.
[19] I. Wagner, H. Musso, *Angew Chem* **1983**, *22*(11), 816.
[20] M. A. T. Blaskovich, *J. Med. Chem.* **2016**, *59*(24), 10807.
[21] S. M. So, H. Kim, L. Mui, J. Chin, *Eur. J. Org. Chem.* **2012**, *2*, 229.
[22] F. Lovering, *Med Chem Commun* **2013**, *4*, 515.
[23] K. Fosgerau, T. Hoffmann, *Drug Discovery Today* **2015**, *20*, 122.
[24] A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, *61*(4), 1382.
[25] H. Mei, J. Han, K. D. Klika, K. Izawa, T. Sato, N. A. Meanwell, V. A. Soloshonok, *Eur. J. Med. Chem.* **2020**, *186*, 111826.
[26] H. Shinkai, M. Nishikawa, Y. Sato, K. Toi, I. Kumashiro, Y. Seto, M. Fukuma, K. Dan, S. Toyoshima, *J. Med. Chem.* **1989**, *32*, 1436.
[27] C. Lin, A. D. Kwong, R. B. Perni, *Infect Disord Drug Targets* **2006**, *6*(1), 3.
[28] R. A. Feelders, U. Yasothan, P. Kirkpatrick, *Nat. Rev. Drug Discovery* **2012**, *11*, 597.
[29] A. H. Gouliaev, A. Senning, *Brain Res Rev* **1994**, *19*(2), 180.
[30] A. D. Baylis, *Pest Manage. Sci.* **2000**, *56*(4), 299.
[31] F. E. Dayan, C. L. Cantrell, S. O. Duke, *Bioorg. Med. Chem.* **2009**, *17*(12), 4022.
[32] H. Katsuta, M. Nomura, T. Wakita, H. Daido, Y. Kobayashi, A. Kawahara, S. Banba, *J. Pestic. Sci.* **2019**, *44*(2), 120.

[33] Y. Ozoe, T. Kita, F. Ozoe, T. Nakao, K. Sato, K. Hirase, *Pestic. Biochem. Physiol.* **2013**, *107*(3), 285.
[34] T. Nakao, S. Banba, *Bioorg. Med. Chem.* **2016**, *24*(3), 372.
[35] T. Selby, K. Sun, *WO 2002032856*, **2002**.
[36] T. M. Stevenson, *WO 2003103398*, **2003**.
[37] W. Dong, J. Xu, L. Xiong, Z. Li, *J. Iran. Chem. Soc.* **2013**, *10*, 429.
[38] J. Li, Z. Zhang, X. Xu, X. Shao, Z. Li, *Aust. J. Chem.* **2015**, *68* (10), 1543.
[39] Y. Liu, C. Lei, X. Xu, X. Shao, Z. Li, *Chin. Chem. Lett.* **2015**, *27* (3), 321.
[40] Y. Liu, X. Chen, X. Xu, J. Cheng, X. Shao, Z. Li, *Lett. Drug Des. Discovery* **2017**, *14*(3), 262.
[41] B. Chai, B. Li, H. Wu, D. Xiang, H. Yang, H. Yu, J. Yuan, H. Zhang, *WO 2008134969*, **2008**.
[42] R. Ghadari, F. S. Alavi, M. Zahedi, *Comput. Biol. Chem.* **2015**, *56*, 33.
[43] A. Saeed, D. Shahzad, M. Faisal, F. A. Larik, H. R. EI-Seedi, P. A. Channar, *Chirality* **2017**, *19*(11), 1.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Chen R-J, Wang J-J, Han L, et al. Design, synthesis, and insecticidal activities of novel diamide derivatives with alpha-amino acid subunits. *J Heterocyclic Chem*. 2021; 1–8. https://doi.org/10.1002/jhet.4268