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Synthesis and biological activities of novel 1,3,4-thiadiazole-containing pyrazole oxime derivatives

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ABSTRACT

A new library of 1,3,4-thiadiazole-containing pyrazole oximes were designed and synthesized. Their acaricidal and insecticidal activities were evaluated. Bioassay results indicated that some target compounds exhibited good acaricidal and insecticidal properties. Especially, compound **8m** had 80% acaricidal activity against *Tetranychus cinnabarinus* at the concentration of 50 μg/mL, compound **8f** displayed 100% insecticidal activities against *Aphis craccivora* at the concentration of 50 μg/mL, compounds **8r** and **8w** showed 100% insecticidal activities against *Plutella xylostella* at the concentration of 50 μg/mL. Furthermore, compounds **8r** (LC_{50} = 19.61 μg/mL) and **8w** (LC_{50} = 9.78 μg/mL) possessed comparable or even better insecticidal activities than the control Pyridalyl (LC_{50} = 17.40 μg/mL) against *Plutella xylostella*.

Keywords: 1,3,4-Thiadiazole, Pyrazole oxime, Synthesis, Bioactivity

In recent years, the development of heterocyclic agrochemicals has become a main trend for their flexible structure, low mammalian toxicity, and high activity in the research on pesticides. As an important five-member of heterocycle, literature survey has been revealed that 1,3,4-thiadiazole derivatives possess broad spectrum biological activities such as insecticidal,[1,2] fungicidal,[3,4] and herbicidal activity.[5] At present, many commercial marketed pesticides such as *Tebuthiuron* and

Thiazafluron (Figure 1), containing a 1,3,4-thiadiazole ring, have been widely used in agriculture. Furthermore, the research of 1,3,4-thiadiazole compounds in medicinal and pharmaceutical chemistry is also unfolded rapidly.[6] Many 1,3,4-thiadizole-containing compounds are found to possess potent anticancer,[7,8] and anti-proliferative activity.[9] This endowed a great impetus to the study of biologically active 1,3,4-thiadiazole derivatives.

On the other hand, pyrazole oxime unit plays a vital role in bioactive molecules. Lots of pyrazole oxime derivatives are reported to possess diverse bioactivities including fungicidal,[10] insecticidal,[11] acaricidal,[12] anti-TMV,[13] and antitumor properties.[14] For example, Fenpyroximate (Figure 1), an excellent acaricide bearing a pyrazole oxime unit, is used to control some phytophagous mites such as *Tetranychus urticae* Koch and *Polyphagotarsonemus latus* Banks.[15,16] Furthermore, a series of Fenpyroximate analogues have displayed satisfactory antitumor activity.[17] Recently, Dai and co-workers have obtained a variety of novel pyrazole oxime derivatives by replacing the esterified aryl group of Fenpyroximate with different heterocycles such as thiazole,[18] pyridine,[19] and oxazole ring.[20] Some of them exhibited promising fungicidal activity beyond good insecticidal and acaricidal activity. Very recently, Dai et al. also found some pyrazole oximes possessed interesting insecticidal activity besides potent acaricidal activity through modification of the esterified group of Fenpyroximate with thiazolylmethoxy unit.[21] Thus, we have reason to believe that the pyrazole oxime moiety can be used as a significant skeleton in exploring new bioactive compounds.

Considering the facts mentioned above, we speculated that the introduction of a substituted 1,3,4-thiadiazole pharmacophore into pyrazole oximes might produce some new compounds with multiple bioactivities. Herein, we describe the design and synthesis of a series of novel pyrazole

oximes carrying a substituted 1,3,4-thiadiazole ring. Moreover, all the new compounds were investigated for their acaricidal and insecticidal activities.

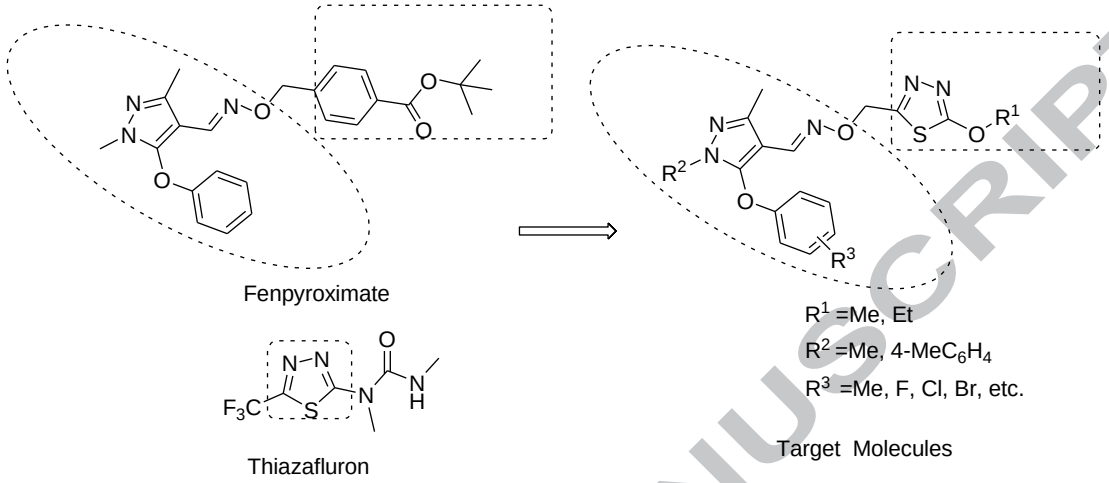
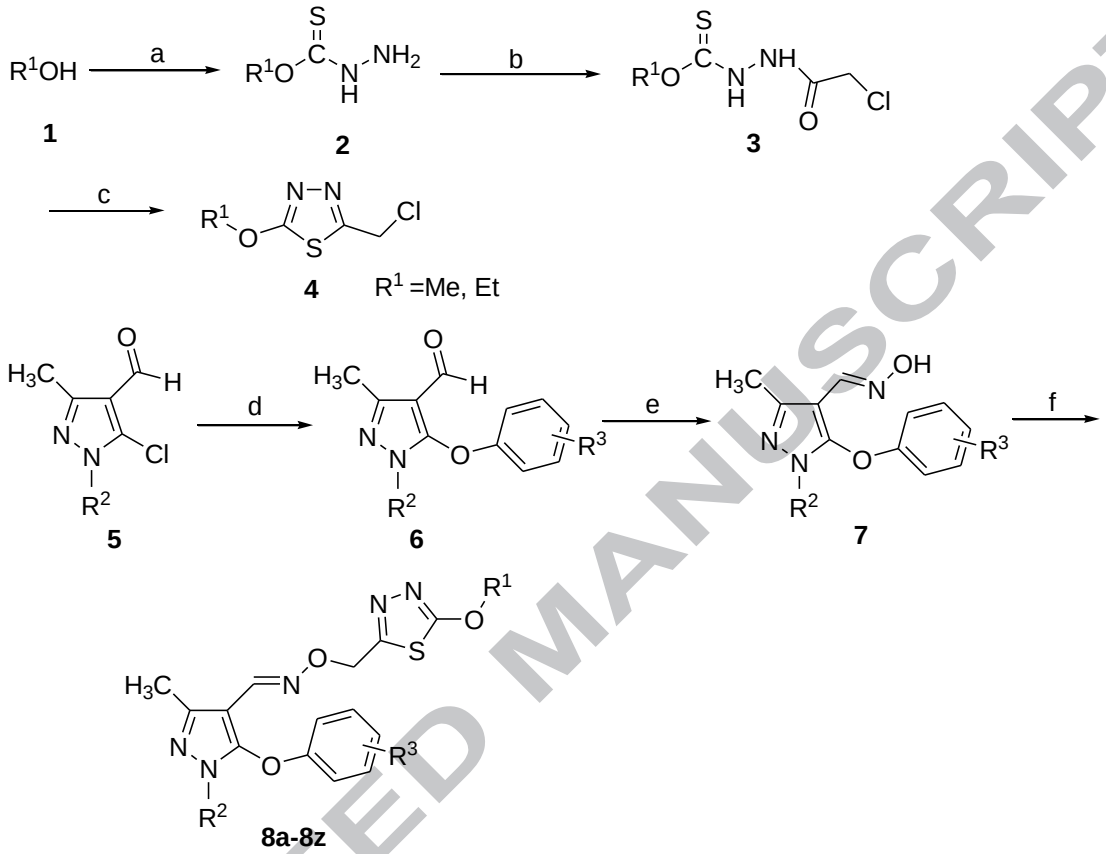


Figure 1. The design of the target molecules.

The general synthetic route of the target compounds **8a-8z** was outlined in Scheme 1. Intermediate 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole (**4**) was synthesized from alcohols (**1**). Compound **1** reacted with carbon disulfide under basic condition, and further subjected to hydrazinolysis to give intermediate **2**.[22] The condensation of compound **2** with chloracetyl chloride produced compound **3** successfully, which was then cyclized to form 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole (**4**). 5-aryloxy pyrazole oximes (**7**) were prepared from compound **5**. Introduction of substituted phenols into 5-chloropyrazole-4-carbaldehyde (**5**) by nucleophilic aromatic substitution gave 5-aryloxy substituted pyrazole carbaldehyde (**6**) successfully.[23] Further reaction of 5-aryloxypyrazole carbaldehyde (**6**) with hydroxylamine hydrochloride in methanol or ethanol medium afforded 5-aryloxy pyrazole oximes (**7**) in satisfactory yields. The treatment of intermediate **7** with 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole (**4**) in acetonitrile medium using potassium carbonate as alkali produced corresponding pyrazole oximes containing a substituted 1,3,4-thiadiazole moiety smoothly (Scheme 1). The structures of the newly synthesized compounds **8a-8z** were well

characterized by ^{1}H NMR, ^{13}C NMR, and elemental analyses (detailed information see Supplementary data).



Scheme 1. Synthesis of compounds **8a-8z**. Reagents and conditions: (a) (i) CS_2, NaOH-H_2O, 20 °C, 3 h; (ii) NH_2NH_2-H_2O, 30 °C, 2 h; (b) CH_3COONa-H_2O, 1,4-dioxane, chloroacetyl chloride, 0 °C to rt, 4 h; (c) H_2SO_4, 0 °C, 3 h; (c) substituted phenols, KOH, DMF or DMSO, 45 °C, 2 h, 110 °C, 6-22 h; (e) $NH_2OH{\cdot}HCl$, KOH, CH_3OH or CH_3CH_2OH, reflux, 5-20 h; (f) compound **4**, K_2CO_3, CH_3CN, reflux, 8-17 h.

In this study, the title compounds **8a-8z** were tested for their insecticidal activities against *Aphis craccivora* and *Plutella xylostella* and acaricidal activity against *Tetranychus cinnabarinus* using known procedures,[24-26] and Imidacloprid, Pyridalyl and Fenpyroximate were used as the positive controls, respectively. As shown in Table 1, some title compounds possessed excellent acaricidal activities against *T. cinnabarinus* at a concentration of 200 μg/mL. For instance, the mortalities of compounds **8m**, **8n**, **8p**, **8r**, **8s**, and **8t** against *T. cinnabarinus* were 100%, 100%, 100%, 95%, 100%, and 100%, respectively, which were similar to that of the control Fenpyroximate. Some of them displayed good acaricidal properties against *T. cinnabarinus* when the concentration was

reduced to 100 μg/mL, compounds **8m**, **8n**, **8p**, **8r**, **8s**, and **8t** had 100%, 100%, 90%, 80%, 80%, and 80% inhibition rates, respectively. Among them, compounds **8m**, **8s**, and **8t** were still active against *T. cinnabarinus* even when the concentration was reduced to 50 μg/mL with inhibitory values of 80%, 50%, and 65%, respectively. Based on the structure-potency data, we can find that when R^1 is Me and R^2 is Me, most of the target compounds showed no acaricidal activity against *T. cinnabarinus* except compound **8a** possessing 60% morality at 200 μg/mL. When R^1 is ethyl (R^2=Me), some designed compounds displayed relatively better acaricidal activity against *T. cinnabarinus* than did the corresponding methyl derivatives (R^2=Me). For example, compounds **8a**, **8b**, **8e**, **8f**, **8l**, **8n**, **8r**, and **8s** exhibited 60%, 0%, 0%, 0%, 80%, 100%, 95%, and 100% acaricidal activity against *T. cinnabarinus* at the concentration of 200 μg/mL, respectively. Moreover, we can also see that when R^1 is ethyl (R^2=Me), the substituent at 4-position of phenyl ring was halogen (**8s** and **8t**) or trifluoromethoxy (**8m**), it was advantageous to increase the acaricidal activity at 50 μg/mL except 4-fluoro derivative (**8q)**. From the data presented in Table 1, we found that most of the obtained compounds displayed perfect insecticidal activities against *A. craccivora* at the concentration of 200 μg/mL. Furthermore, some of them showed good insecticidal activities against *A. craccivora* when the concentration was lowered to 100 μg/mL, compounds **8f**, **8j**, **8l**, **8m**, **8n**, **8p**, **8r**, **8s**, and **8t** possessed 100%, 100%, 95%, 100%, 90%, 100%, 90%, 100%, and 95% inhibition rates, respectively, which were comparable to that of the control Imidacloprid. Interestingly, even when the concentration was reduced to 50 μg/mL, compounds **8f**, **8l**, **8m**, **8p**, **8r**, **8s**, and **8t** showed 100%, 90%, 95%, 95%, 90%, 95%, and 90% insecticidal activities against *A. craccivora*, respectively, which were similar to that of the control Imidacloprid. From the above insecticidal activity data, we can infer that the substituents on the

benzene ring also have an impact on the activities, when 3- or 4-position of phenyl ring bears a halogen atom (**8f**, **8l**, **8p**, **8r**, **8s**, and **8t**), methoxy (**8l**) or trifluoromethoxy (**8m**), it would be more favorable to the insecticidal activities against *A. craccivora* except compounds **8e** and **8q**. Table 1 exhibited that some of the designed compounds had satisfactory insecticidal activities against *P. xylostella* beyond good insecticidal activities against *A. craccivora*. For example, the mortalities of compounds **8l**, **8m**, **8n**, **8p**, **8q**, **8r**, **8s**, **8t**, **8v**, and **8w** against *P. xylostella* were all 100% at 200 μg/mL, which were similar to that of the control Pyridalyl. Moreover, the insecticidal activities of compounds **8r** (100%) and **8w** (100%) against *P. xylostella* at 50 μg/mL even reached the level of Pyridalyl (100%). From the data listed in Table 1, we can find that structure-insecticidal activity relationship of some compounds against *P. xylostella* were similar to structure-acaricidal activity relationship against *T. cinnabarinus*. When R^1 is ethyl (R^2=Me), some title compounds showed relatively higher insecticidal activity against *P. xylostella* than did the corresponding methyl derivatives (R^2=Me), and 3-, 4- or 2, 4-position of phenyl ring possessing methoxy (**8l**), hydrogen (**8n**) or halogen (**8p**, **8q**, **8r**, **8s**, **8t**, **8v**, and **8w**) was more favorable to the insecticidal activity against *P. xylostella* at 50 μg/mL than other substituents. When R^2 is 4-MeC_6H_4 (R^1=Et), compounds **8y** and **8z** displayed poor insecticidal activities against *A. craccivora* and *P. xylostella* at the concentration of 200 μg/mL, which were lower than those of compounds **8q** and **8s** (R^2=Me and R^1=Et). The data presented in Table 1 also showed that 4-chloro substituted compound **8s** and 4-bromo substituted analogue **8t** possessed good insecticidal activities against *P. xylostella* and *A. craccivora* beyond potent acaricidal properties against *T. cinnabarinus* from the concentrations of 200 μg/mL to 50 μg/mL. In addition, Table 2 indicated the results of further toxicity assay about the typical candidates **8q**, **8r** and **8w**, and the control Pyridalyl against *P. xylostella*. The data listed

in Table 2 displayed that compounds **8r** and **8w** had good potency against *P. xylostella*, and the 50% lethal concentration (LC_{50}) values of compounds **8r** and **8w** were 19.61 and 9.78 μg/mL, respectively, which were comparable or even better than that of the control Pyridalyl (LC_{50} = 17.40 μg/mL). All the above data implied that the biological activity spectrum of pyrazole oxime derivatives was importantly improved via the introduction of a substituted 1,3,4-thiadiazole ring. These studies represent a significant basis for the development of novel pesticides in future.

Table 1. Insecticidal and acaricidal activities of compounds **8a**-**8z** (mortality, %)

Compd.	R^1	R^2	R^3	*Aphis craccivora*			*Tetranychus cinnabarinus*			*Plutella xylostellas*		
				200 μg/mL	100 μg/mL	50 μg/mL	200 μg/mL	100 μg/mL	50 μg/mL	200 μg/mL	100 μg/mL	50 μg/mL
8a	Me	Me	4-OMe	100	60	0	60	0	—	65	30	0
8b	Me	Me	-H	100	30	—	0	—	—	0	—	—
8c	Me	Me	2-F	100	50	—	0	—	—	0	—	—
8d	Me	Me	2-Cl	100	70	0	0	—	—	60	0	—
8e	Me	Me	3-Cl	100	40	—	0	—	—	71	0	—
8f	Me	Me	4-Cl	100	100	100	0	—	—	71	60	0
8g	Me	Me	3,4-diMe	80	0	—	0	—	—	0	—	—
8h	Me	Me	2,4-diF	50	0	—	0	—	—	0	—	—
8i	Me	Me	2,4-diCl	100	30	—	0	—	—	60	0	—
8j	Et	Me	3-Me	100	100	0	0	—	—	45	—	—
8k	Et	Me	4-Me	100	80	65	60	0	—	86	45	30
8l	Et	Me	4-OMe	100	95	90	80	40	—	100	100	60
8m	Et	Me	4-OCF_3	100	100	95	100	100	80	100	60	15
8n	Et	Me	-H	100	90	70	100	100	0	100	71	45
8o	Et	Me	2-F	100	80	0	60	0	—	86	45	—
8p	Et	Me	3-F	100	100	95	100	90	0	100	100	71
8q	Et	Me	4-F	100	50	0	0	—	—	100	71	60
8r	Et	Me	3-Cl	100	90	90	95	80	0	100	100	100
8s	Et	Me	4-Cl	100	100	95	100	80	50	100	86	71
8t	Et	Me	4-Br	100	95	90	100	80	65	100	100	86
8u	Et	Me	3-NO_2	90	65	0	0	—	—	45	—	—
8v	Et	Me	2,4-diF	80	40	—	0	—	—	100	86	45
8w	Et	Me	2,4-diCl	90	50	—	0	—	—	100	100	100
8x	Et	Me	6-Cl-3-Me	100	70	20	70	0	—	86	30	—
8y	Et	4-MeC_6H_4	4-F	30	—	—	0	—	—	10	—	—
8z	Et	4-MeC_6H_4	4-Cl	20	—	—	0	—	—	0	—	—
Imidacloprid				100	100	100	—	—	—	—	—	—
Fenpyroximate				—	—	—	100	100	100	—	—	—
Pyridalyl				—	—	—	—	—	—	100	100	100

"—" refers to "not tested".

Table 2. Toxicities of compounds **8q**, **8r**, and **8w**, and Pyridalyl against *Plutella xylostella*

Compd.	regression equation	LC_{50}[a] (μg/mL)	r[b]
8q	Y = 1.51 + 2.70x	33.75	0.9986
8r	Y = 1.22 + 3.43x	19.61	0.9978
8w	Y = 1.25 + 3.76x	9.78	0.9907
Pyridalyl	Y = 2.22 + 2.24X	17.40	0.9981

[a] LC_{50} refers to median lethal concentration.

[b] r refers to correlative coefficient.

In summary, a series of pyrazole oxime derivatives bearing a 1,3,4-thiadiazole moiety have been synthesized and evaluated for their acaricidal activity against *T. cinnabarinus*, and insecticidal activities against *A. craccivora* and *P. xylostella*. Some of the derivatives displayed good acaricidal and insecticidal properties. Among these compounds, compound **8m** showed 80% acaricidal activity against *T. cinnabarinus* at the concentration of 50 μg/mL, compound **8f** possessed 100% insecticidal activities against *A. craccivora* at the concentration of 50 μg/mL, compounds **8r** and **8w** had 100%, and 100% insecticidal activities against *P. xylostella* at the concentration of 50 μg/mL, respectively. Interestingly, compounds **8s** and **8t** had broad spectrum biological activities, they exhibited satisfactory insecticidal activities against *A. craccivora* and *P. xylostella* besides potential acaricidal activity against *T. cinnabarinus*. Further analogue synthesis and structural optimization are well under way.

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Supplementary data

Supplementary data (which contain information on the synthesis, characterization, and bioactivity test methods of the title compounds) associated with this article can be found, in the online version, at http://dx.doi.org.

References and notes

1 Hu, Y.; Li, C. Y.; Wang, X. M.; Yang, Y. H.; Zhu, H. L. *Chem. Rev*. **2014**, *114*, 5572.

2 Luo, Y. P.; Yang, G. F. *Bioorg. Med. Chem*. **2007**, *15*, 1716.

3 Chen, H.; Li, Z.; Han, Y. *J. Agric. Food Chem.* **2000**, *48*, 5312.

4 Zuo, X.; Mi, N.; Fan, Z. J.; Zheng, Q. X.; Zhang, H. K.; Wang, H.; Yang, Z. K. *J. Agric. Food Chem.* **2010**, *58*, 2755.

5 Li, Z. S.; Wang, W. M.; Lu, W.; Niu, C. W.; Li, Y. H.; Li, Z. M.; Wang, J. G. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 3723.

6 Jain, A. K.; Sharma, S.; Vaidya, A.; Ravichandran, V.; Agrawal, R. K. *Chem. Biol. Drug Des*. **2013**, *81*, 557.

7 Tripathy, R.; Ghose, A.; Singh, J.; Bacon, E. R.; Angeles, T. S.; Yang, S. X.; Albom, M. S.; Aimone, L. D.; Herman, J. L.; Mallamo, J. P. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1793.

8 Polkam, N.; Rayam, P.; Anireddy, J. S.; Yennam, S.; Anantaraju, H. S.; Dharmarajan, S.; Perumalc, Y.; Kotapallid, S. S.; Ummannid, R.; Balasubramanian, S. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 1398.

9 Yadagiri, B.; Gurrala, S.; Bantu, R.; Nagarapu, L.; Poleopalli, S.; Srujana, G.; Jain, N. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 2220.

10 Zhao, P. L.; Wang, L.; Zhu, X. L.; Huang, X.; Zhan, C. G.; Wu, J. W.; Yang, G. F. *J. Am. Chem. Soc.* **2010**, *132*, 185.

11 Fu, C. R.; Pei, J.; Ning, Y.; Liu, M.; Shan, P.; Liu, J.; Hu, F. Z.; Zhu, Y. Q.; Yang, Y.; Zou, X. M. *Pest Manage. Sci.* **2014**, *70*, 1207.

12 Hamaguchi, H.; Kajihara, O.; Katoh, M. *J. Pestic. Sci.* **1995**, *20*, 173.

13 Ouyang, G. P.; Cai, X. J.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D. Y.; Zeng, S. *J. Agric. Food Chem.* **2008**, *56*, 10160.

14 Zheng, L. W.; Li, Y.; Ge, D.; Zhao, B. X.; Liu, Y. R.; Lv, H. S.; Ding, J.; Miao, J. Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4766.

15 Swanson, M. B.; Ivancic, W. A.; Saxena, A. M.; Allton, J. D.; O' Brien, G. K.; Suzuki, T.; Nishizawa, H.; Nokata, M. *J. Agric. Food Chem.* **1995**, *43*, 513.

16 Motoba, K.; Nishizawa, H.; Sukuzi, T.; Hamaguchi, H.; Uchida, M.; Funayama, S. *Pestic. Biochem. Physiol.* **2000**, *67*, 73.

17 Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H.; Lee, K. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307.

18 Dai, H.; Li, Y. Q.; Du, D.; Qin, X.; Zhang, X.; Yu, H. B.; Fang, J. X. *J. Agric. Food Chem.* **2008**, *56*, 10805.

19 Dai, H.; Shi, L.; Zhang, H. J.; Li, Y. Q.; Fang, J. X.; Shi, Y. J. *Chin. J. Org. Chem.* **2012**, *32*, 1060.

20 Wang, S. L.; Shi, Y. J.; He, H. B.; Li, Y.; Li, Y.; Dai, H. *Chin. Chem. Lett.* **2015**, *26*, 672.

21 Dai, H.; Xiao, Y. S.; Li, Z.; Xu, X. Y.; Qian, X. H. *Chin. Chem. Lett.* **2014**, *25*, 1014.

22 Wang, T. T.; Bing, G. F.; Zhang, X.; Qin, Z. F.; Yu, H. B.; Qin, X.; Dai, H.; Fang, J. X. *Chin. J.Org. Chem.* **2009**, *29*, 1287.

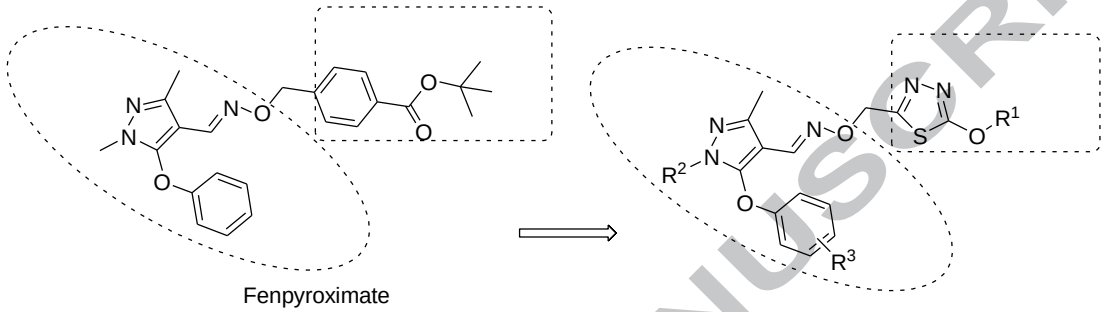
23 Park, M. S.; Park, H. J.; Park, K. H.; Lee, K. I. *Synth. Commun.* **2004**, *34*, 1541.

24 Song, H. J.; Liu, Y. X.; Xiong, L. X.; Li, Y. Q.; Yang, N.; Wang, Q. M. *J. Agric. Food Chem.* **2013**, *61*, 8730.

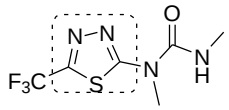
25 Xu, R. B.; Xia, R.; Luo, M.; Xu, X. Y.; Cheng, J. G.; Shao, X. S.; Li, Z. *J. Agric. Food Chem.* **2014**, *62*, 381.

26 Sun, J. L.; Zhou, Y. M. *Molecules* **2015**, *20*, 5625.

The present work reported that the novel pyrazole oximes containing a 1,3,4-thiadiazole moiety are potential candidate structures for new pesticide.



Fenpyroximate



Thiazafluron

8a-**8z**

R^1 =Me, Et

R^2 =Me, 4-MeC_6H_4

R^3 =Me, F, Cl, Br, etc.