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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 was 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 *P. xylostella*.

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* (Fig. 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 (Fig. 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 et al. 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.

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

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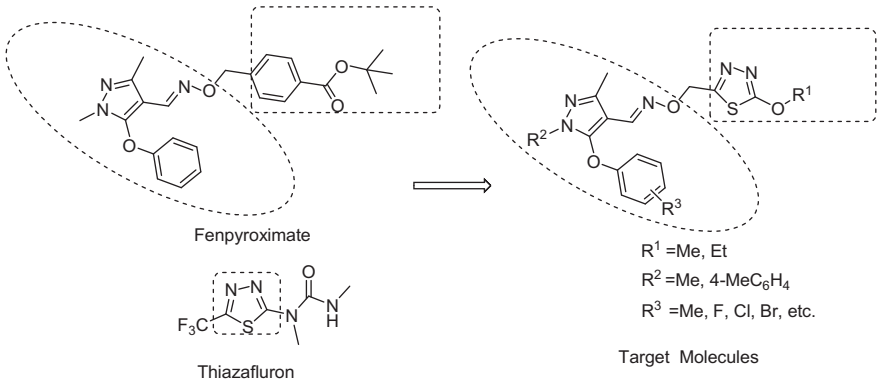
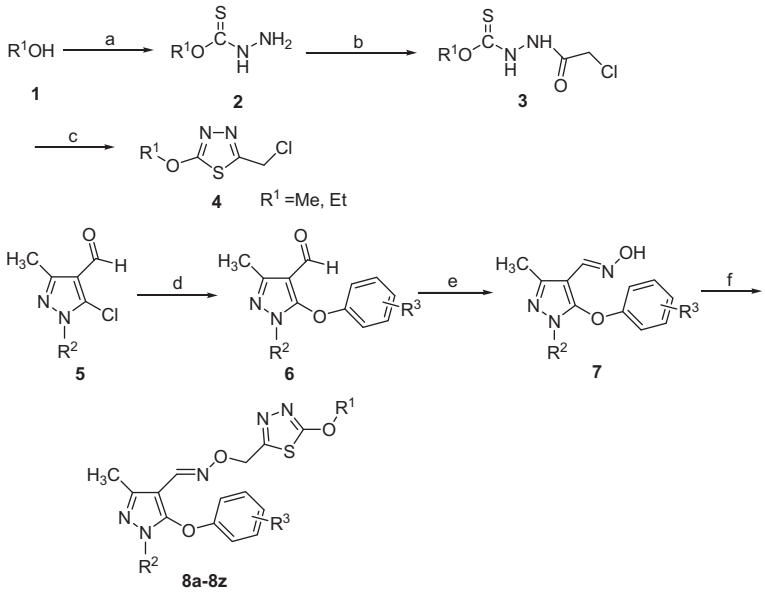


Figure 1. The design of the target molecules.



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·HCl, KOH, CH_3OH or CH_3CH_2OH, reflux, 5–20 h; (f) compound **4**, K_2CO_3, CH_3CN, reflux, 8–17 h.

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).

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.*