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Synthesis and bioactivities of novel pyrazole oxime derivatives containing a 1,2,3-thiadiazole moiety

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ABSTRACT

A series of new pyrazole oxime compounds bearing a 1,2,3-thiadiazole ring were designed, synthesized, and evaluated for their insecticidal, acaricidal and antitumor activities. Bioassays demonstrated that some title compounds displayed satisfactory insecticidal and acaricidal properties. Especially, compounds **8d** and **8h** exhibited 90% insecticidal activities against *Aphis craccivora* at the concentration of 100 μg/mL. Interestingly, some of the target compounds possessed significant antitumor activities against four human cancer cell lines in vitro. Among them, compounds **8e** (IC_{50} = 7.19 μM), **8l** (IC_{50} = 6.56 μM), **8m** (IC_{50} = 8.12 μM), and **8r** (IC_{50} = 7.06 μM) had better inhibitory activities against HCT-116 cells than the control 5-fluorouracil (IC_{50} = 29.50 μM). Additionally, compounds **8j**, **8m**, and **8r** showed wonderful inhibitory activities against SGC-7901 cells with the IC_{50} values of 11.46, 9.41, and 8.64 μM, respectively, which were superior to that of the control 5-fluorouracil.

In the past few decades, heterocycles plays a vital role in the field of agriculture and medicine. Pyrazole is a classical nitrogen-containing heterocycle which extensively exists in natural products and non-natural products.[1,2] Most of these pyrazole derived compounds have been investigated to possess various bioactivities such as insecticidal,[3] acaricidal,[4,5] antibacterial,[6,7] and anticancer activities.[8,9] Pyrazole oxime derivatives are important parts of pyrazole compounds with diverse bioactivities like insecticidal,[10] fungicidal,[11] and anti-tobacco mosaic virus (TMV) activity.[12] For instance, Fenpyroximate (Fig. 1), a potent acaricide carrying a pyrazole oxime in the structure, is widely used in crop protection.[13,14] Furthermore, in 2005 Park et al. also found some Fenpyroximate analogues displayed interesting antitumor activities.[15] This endowed a great impetus to the study of biologically active pyrazole oxime compounds.

On the other hand, as an important five-member heterocycle, 1,2,3-thiadiazole derivatives have also attracted considerable attention due to their versatile bioactivities including fungicidal,[16] insecticidal,[17] and antivirus activities.[18] Recently, Fan et al. reported several series of 1,2,3-thiadiazole derivatives bearing other heterocyclic ring like triazole, and so on, and some of these compounds exhibited good anti-TMV activities.[19,20] More recently, Xu et al. synthesized a series of new 1,2,3-thiadiazoles that displaying perfect antivirus activity against TMV.[21] Additionally, many 1,2,3-thiadiazole containing derivatives are found to exhibit potent antiamoebic,[22] and antitumor property.[23] Therefore, 1,2,3-thiadiazole-based compounds became a focus of chemical and pharmaceutical research.

Inspired by these facts, we envisioned that introduction of a substituted 1,2,3-thiadiazole ring into pyrazole oxime scaffold might produce some compounds possessing a wide spectrum bioactivities. In the present study, we describe the synthesis of a number of novel pyrazole oxime derivatives bearing a 1,2,3-thiadiazole moiety. Moreover, all the title compounds have been investigated for their biological activities containing insecticidal, acaricidal, and antitumor activities.

The synthetic route of the target compounds **8a**–**8t** and **10a**–**10c** was depicted in Scheme 1. The key intermediate 4-alkyl-5-chloromethyl-1,2,3-thiadiazole (**4**) was synthesized from compound **1**. The condensation of intermediate **1** with methyl hydrazinocarboxylate afford compound **2**.[24] Intermediate **2** reacted with thionyl chloride to give compound **3**.[25] Intermediate **3** was treated by two steps including reduction and chlorination to obtain the crucial intermediate 4-alkyl-5-chloromethyl-1,2,3-thiadiazole (**4**). Pyrazole oximes (**7**) and (**9**) were prepared from compound **5**. Intermediate **5** was condensed with sodium substituted phenol at 105 °C to afford 5-aryloxy substituted pyrazole carbaldehyde (**6**),[26] which then reacted with hydroxylamine hydrochloride under basic condition to produce 5-aryloxy pyrazole oximes (**7**) smoothly. Similarly, compound **5** was transformed into 5-chloropyrazole oxime (**9**) by the treatment with hydroxylamine

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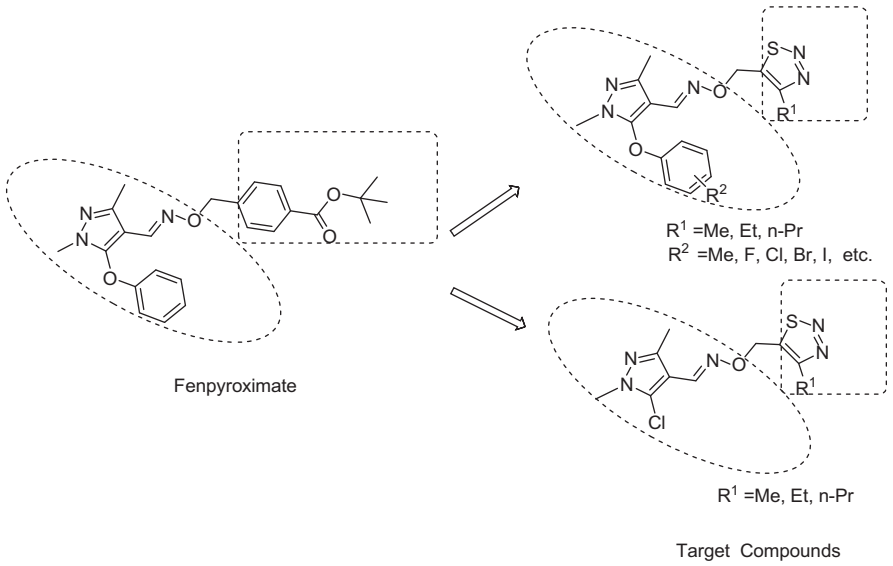
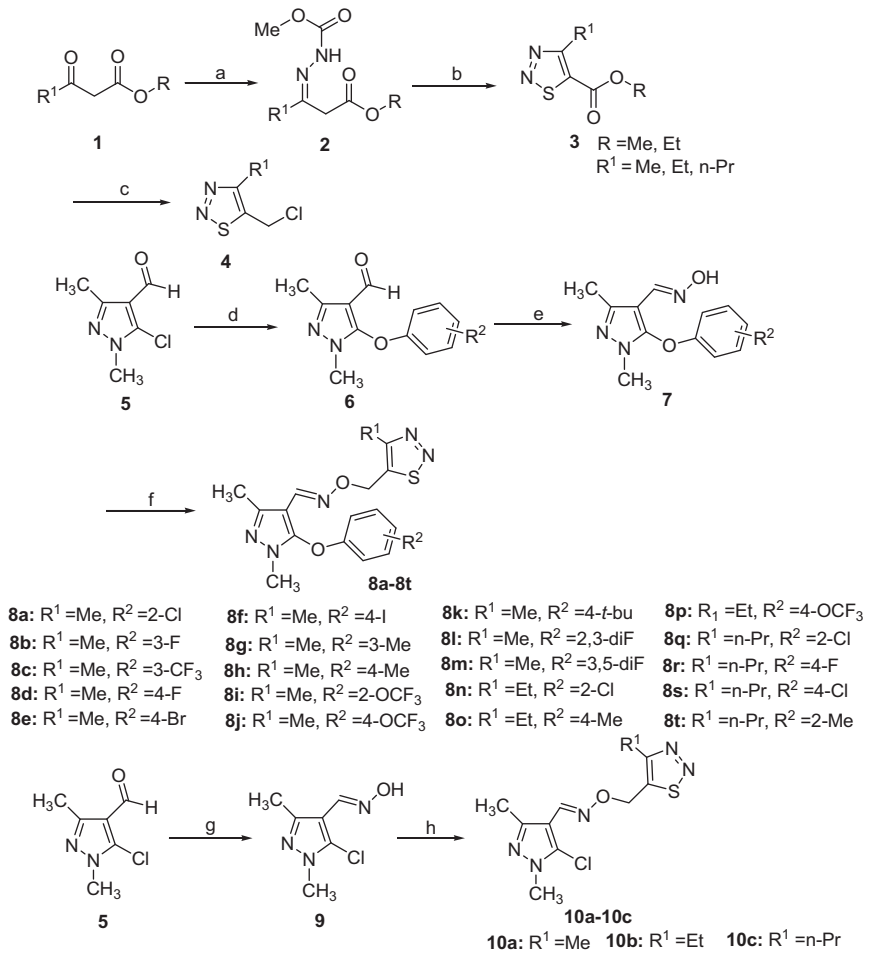


Figure 1. Design of target compounds.



Scheme 1. Synthesis of compounds **8a**–**8t**, **10a**–**10c**. Reagents and conditions: (a) $NH_2NHCOOCH_3$, CH_3CH_2OH, rt, 10 h; (b) $SOCl_2$, CH_2Cl_2, 0 °C to rt, 24 h; (c) (i) $NaBH_4$, I_2, CH_3OH, 0 °C to rt, 3 h; (ii) $SOCl_2$, reflux, 30 min; (d) sodium substituted phenol, DMSO, 105 °C, 8–18 h; (e) $NH_2OH{\cdot}HCl$, KOH, CH_3OH, reflux, 6–17 h; (f) compound **4**, K_2CO_3, CH_3CN, reflux, 7–20 h; (g) $NH_2OH{\cdot}HCl$, KOH, CH_3CH_2OH, reflux, 8 h; (h) compound **4**, K_2CO_3, CH_3CN, reflux, 10–13 h.

hydrochloride. Finally, compound **7** or **9** was admixed with 4-alkyl-5-chloromethyl-1,2,3-thiadiazole (**4**) in CH_3CN using potassium carbonate as alkali to form corresponding pyrazole oximes containing a 1,2,3-thiadiazole moiety successfully.[27] The title compounds have all been confirmed by ^1H NMR, ^{13}C NMR, and elemental analyses (detailed information see Supplementary data).