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

Hong Dai, Shushan Ge, Gang Li, Jia Chen, Yujun Shi, Linyu Ye, Yong Ling

PII: S0960-894X(16)30796-X
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.07.068
Reference: BMCL 24112

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 7 May 2016
Revised Date: 8 July 2016
Accepted Date: 28 July 2016

Please cite this article as: Dai, H., Ge, S., Li, G., Chen, J., Shi, Y., Ye, L., Ling, Y., Synthesis and bioactivities of novel pyrazole oxime derivatives containing a 1,2,3-thiadiazole moiety, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.07.068

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

Hong Dai [a,b], Shushan Ge [b], Gang Li [a], Jia Chen [a], Yujun Shi [a,*], Linyu Ye [a], Yong Ling [b,*]

[a] *College of Chemistry and Chemical Engineering, Nantong University, Nantong 226019, People's Republic of China*

[b] *School of Pharmacy, Nantong University, Nantong 226001, People's Republic of China*

Corresponding Author Emails: yjshi2015@163.com; yling2015@aliyun.com;

Tel: +86-513-85012851

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.

Keywords: Pyrazole oxime, 1,2,3-Thiadiazole, Synthesis, Bioactivity

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 (Figure 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.

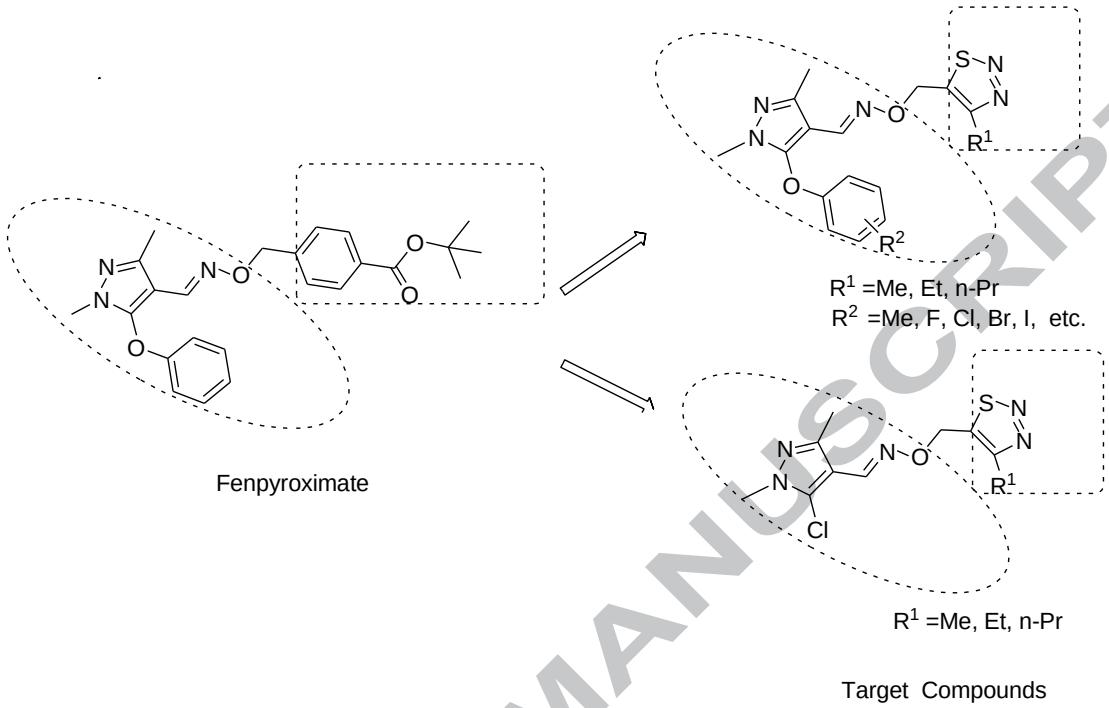
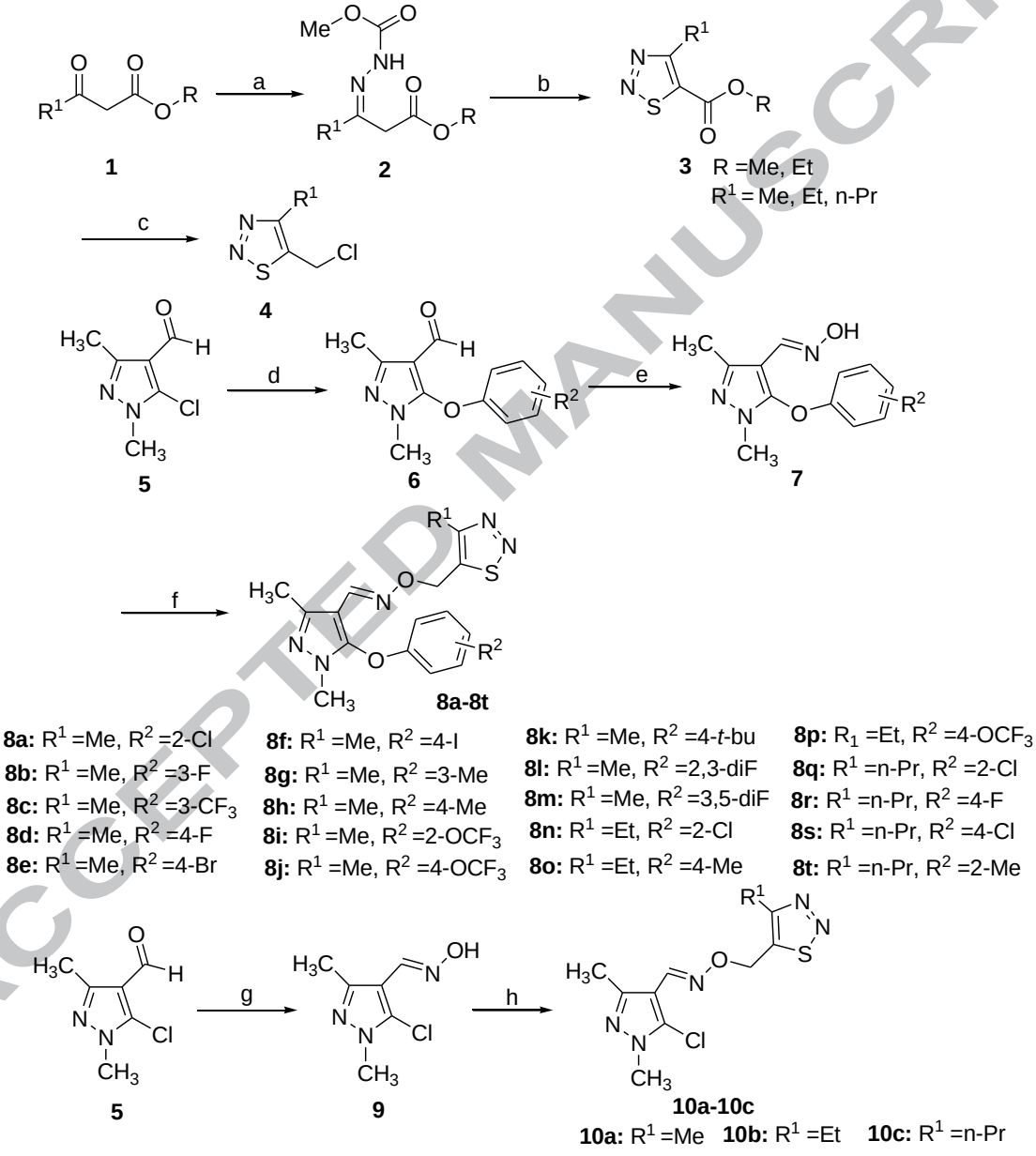


Figure 1. Design of target compounds.

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 ^{o}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 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).



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.

The synthesized compounds **8a**-**8t** and **10a**-**10c** were evaluated for insecticidal activities against *Plutella xylostella* and *Aphis craccivora*, and acaricidal activity against *Tetranychus cinnabarinus* using known procedures,[28-30] and Pyridalyl, Imidacloprid and Fenpyroximate were used as the positive controls, respectively. As shown in Table 1, some of the target compounds exhibited excellent insecticidal activities against *Plutella xylostella* at a concentration of 200 μg/mL. For instance, the mortalities of compounds **8a**, **8d**, **8e**, **8h**, **8k**, **8l**, **8m**, and **10a** against *P. xylostella* were all 100%, which were similar to that of the control Pyridalyl. Some of them displayed good insecticidal properties against *P. xylostella* when the dosage was reduced to 100 μg/mL, compounds **8e** and **8f** had 80% and 62% inhibition rates, respectively. Compounds **8e** and **8f** were still active against *P. xylostella* even when the dosage was lowered to 50 μg/mL with inhibitory values of 43% and 60%, respectively. Based on the structure-insecticidal activity data, we found that when R^1 is Et or n-Pr, all of the target compounds showed no insecticidal activity against *P. xylostella* at 200 μg/mL. When R^1 is Me, some designed compounds had better insecticidal activity against *P. xylostella* than did the corresponding ethyl and n-propyl derivatives. For example, compounds **8a**, **8n**, **8q**, **10a**, **10b**, and **10c** possessed 100%, 0%, 0%, 100%, 0%, and 0% insecticidal activity against *P. xylostella* at the concentration of 200 μg/mL, respectively. In addition, we can also see that when R^1 is Me, the substituent at 2-, 4-, 2,3- or 3,5-position of phenyl ring was halogen (**8a**, **8d**, and **8e**) or the substituent at 4-position of phenyl ring was alkyl (**8h** and **8k**), it was advantageous to increase the insecticidal activity at 200 μg/mL. Meanwhile, some designed compounds displayed good insecticidal properties against *A. craccivora* besides satisfactory insecticidal activity against *P. xylostella*. For example, compounds **8b**, **8d**, **8f**, **8g**, **8h**, **8j**, **8k**, **8m**, and **10a** had 98%, 99%, 95%, 90%, 100%, 100%, 95%, 90%, and 100% insecticidal

activity against *A. craccivora* at the concentration of 200 μg/mL, respectively, which were equally to that of the control Imidacloprid. Moreover, compounds **8b**, **8d**, **8h**, **8j**, **8k**, and **10a** showed significant insecticidal activity against *A. craccivora* at the concentrations of 100 μg/mL and 50 μg/mL. At the concentration of 100 μg/mL, **8d** and **8h** possessed 90% and 90% inhibitory rates, respectively, which were similar to that of Imidacloprid. From the data presented in Table 1, we can find that structure-insecticidal activity relationship of some derivatives against *A. craccivora* was similar to structure-insecticidal activity relationship against *P. xylostella*. When R^1 is Me, some designed compounds displayed relatively higher insecticidal activity against *A. craccivora* than did the corresponding ethyl and n-propyl derivatives, and 3-, 4-, or 3,5-position of phenyl ring bearing halogen (**8b**, **8d**, **8f**, and **8m**), alkyl (**8g**, **8h**, and **8k**) or trifluoromethoxy (**8j**) was more favorable to the insecticidal activity against *A. craccivora* at 100 μg/mL and 50 μg/mL than other substituents. Meanwhile, Table 1 also indicated that some target compounds possessed good acaricidal activities against *T. cinnabarinus* at 200 μg/mL. For instance, the mortalities of compounds **8b**, **8f**, and **8j** against *T. cinnabarinus* were 80%, 90%, and 80%, respectively, which were similar to that of the control Fenpyroximate. Additionally, compounds **8b** and **8f** were still active against *T. cinnabarinus* when the concentration was lowered to 100 μg/mL with inhibitory rates of 50% and 60%, respectively. The data listed in Table 1 showed that 4-iodo substituted compound **8f** had potent insecticidal properties against *P. xylostella* and *A. craccivora* beyond moderate acaricidal activities against *T. cinnabarinus* at the concentrations of 200 μg/mL and 100 μg/mL.

The cytotoxicity of target compounds **8a-8t** and **10a-10c** against human pancreatic carcinoma cells (Panc-1), human hepatoma cells (Huh-7), human colon cancer cells (HCT-116) and human

gastric cancer cells (SGC-7901) were tested in vitro by MTT method[31] using sorafenib, cisplatin, and 5-fluorouracil as the positive controls, respectively. The IC_{50} values were summarized in Table 2. As can be seen, compounds **8e** and **8l** exhibited optimal activity with IC_{50} values of 12.79, 12.22, 11.84, and 10.17 μM in Panc-1 and Huh-7 cells, respectively, which were comparable to those of the controls sorafenib (11.50 μM) and cisplatin (12.70 μM). The cytotoxicity of most compounds against HCT-116 cells was similar or superior to that of the control 5-fluorouracil. Among them, compounds **8e**, **8l**, **8m**, and **8r** (IC_{50} = 7.19, 6.56, 8.12, and 7.06 μM, respectively) showed stronger antiproliferative effects than 5-fluorouracil (IC_{50} = 29.50 μM). Table 2 also displayed that some derivatives expressed important antitumor activity against SGC-7901 cell lines. Especially, the IC_{50} values of **8c**, **8e**, **8g**, **8h**, **8j**, **8m**, **8n**, **8p**, **8q**, **8r**, **8s**, and **8t** were 12.39, 15.15, 12.75, 12.80, 11.46, 9.41, 15.79, 13.59, 17.62, 8.64, 18.55, and 16.26 μM, respectively, which were better than that of 5-fluorouracil (56.12 μM). The data presented in Table 2 exhibited that 4-bromo substituted compound **8e** and 2,3-difluoro substituted analogue **8l** possessed more potent inhibitory activity against all tested cancer cells. All the above results suggested that appreciable biological activities can be achieved through introducing the 1,2,3-thiadiazole group into pyrazole oxime heterocyclic system. Meanwhile, this study also offers a significant basis for the design of novel molecules with wide spectrum bioactivities.

In summary, a variety of new pyrazole oxime compounds carrying a 1,2,3-thiadiazole moiety were designed and synthesized. Bioassays revealed that some of the designed compounds displayed good insecticidal properties against *P. xylostella* and *A. craccivora* besides potential acaricidal activities against *T. cinnabarinus*. Moreover, some title compounds exhibited satisfactory antitumor activities against four cancer cells. Particularly, compounds **8e**, **8l**, **8m**, and

8r expressed excellent inhibitory activities against HCT-116 cells with IC_{50} values of 7.19, 6.56, 8.12, and 7.06 μM, respectively, which were better than that of 5-fluorouracil (29.50 μM), and compounds **8j**, **8m**, and **8r** showed much higher anticancer activities against SGC-7901 cells than the control 5-fluorouracil. Further studies on these compounds are in progress in our laboratory.

Table 1. Insecticidal and acaricidal activities of compounds **8a-8t** and **10a-10c** (mortality, %)

Compd.	*P. xylostella*			*A. craccivora*			*T. cinnabarinus*		
	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	100	0	—	15	—	—	0	—	—
8b	71	0	—	98	80	52	80	50	0
8c	45	—	—	62	55	31	0	—	—
8d	100	0	—	99	90	60	0	—	—
8e	100	80	43	20	—	—	0	—	—
8f	64	62	60	95	70	41	90	60	0
8g	84	0	—	90	70	38	0	—	—
8h	100	0	—	100	90	58	0	—	—
8i	66	0	—	22	—	—	0	—	—
8j	50	0	—	100	85	59	80	—	—
8k	100	0	—	95	80	50	0	—	—
8l	100	0	—	19	—	—	0	—	—
8m	100	0	—	90	75	45	0	—	—
8n	0	—	—	0	—	—	0	—	—
8o	0	—	—	0	—	—	0	—	—
8p	0	—	—	0	—	—	0	—	—
8q	0	—	—	0	—	—	0	—	—
8r	0	—	—	0	—	—	0	—	—
8s	0	—	—	0	—	—	0	—	—
8t	0	—	—	0	—	—	0	—	—
10a	100	0	—	100	85	61	0	—	—
10b	0	—	—	0	—	—	0	—	—
10c	0	—	—	0	—	—	0	—	—
Pyridalyl	100	100	100	—	—	—	—	—	—
Imidacloprid	—	—	—	100	100	100	—	—	—
Fenpyroximate	—	—	—	—	—	—	100	100	100

"—" refers to "not tested".

Table 2 Antitumor activity of compounds **8a-8t and 10a-10c.**

Compd	IC_{50}, μM			
	Panc-1	HUH-7	HCT-116	SGC-7901
8a	>50	>50	42.53	>50
8b	>50	>50	>50	>50
8c	>50	>50	10.30	12.39
8d	>50	>50	30.16	>50
8e	12.79	11.84	7.19	15.15
8f	>50	>50	43.82	>50
8g	>50	>50	14.10	12.75
8h	>50	>50	13.81	12.80
8i	>50	>50	>50	>50
8j	>50	>50	12.82	11.46
8k	>50	>50	33.54	>50
8l	12.22	10.17	6.56	25.65

8m	>50	>50	8.12	9.41
8n	>50	>50	17.60	15.79
8o	>50	>50	>50	19.80
8p	>50	>50	12.50	13.59
8q	>50	>50	16.41	17.62
8r	>50	>50	7.06	8.64
8s	>50	>50	19.21	18.55
8t	>50	>50	15.68	16.26
10a	26.56	>50	>50	>50
10b	>50	>50	>50	>50
10c	>50	>50	>50	>50
5-Fluorouracil	—	—	29.50	56.12
Cisplatin	—	12.70	—	—
Sorafenib	11.50	—	—	—

"—" refers to "not tested".

Acknowledgments

This work was funded by the National Natural Science Foundation of China (Nos. 21202089, 21372135), the Research Foundation of the Six People Peak of Jiangsu Province (No. 2013-SWYY-013), the Technology Project Fund of Nantong City (Nos. AS2014011, CP12013002, MS22015020).

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. Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. *Eur. J. Med. Chem.* **2013**, *69*, 735.
2. Küçükgüzel, Ş. G.; Şenkardeş, S. *Eur. J. Med. Chem.* **2015**, *97*, 786.
3. Wu, J.; Song, B. A.; Hu, D. Y.; Yue, M.; Yang, S. *Pest Manag. Sci.* **2012**, *68*, 801.

4. Li, M.; Liu, C. L.; Li, L.; Yang, H.; Li, Z. N.; Zhang, H.; Li, Z. M. *Pest Manag. Sci.* **2010**, *66*, 107.

5. Furuya, T.; Akiyuki, S. U. W. A.; Nakano, M.; Fujioka, S.; Yasokawa, N.; Machiya, K. *J. Pest. Sci.* **2015**, *40*, 38.

6. Rahimizadeh, M.; Pordel, M.; Bakavoli, M.; Rezaeian, S.; Sadeghian, A. *World J. Microb. Biot.* **2010**, 26, 317.

7. Mert, S.; Kasımoğulları, R.; Iça, T.; Çolak, F.; Altun, A.; Ok, S. *Eur. J. Med. Chem*. **2014**, *78*, 86.

8. Nitulescu, G. M.; Draghici, C.; Missir, A. V. *Eur. J. Med. Chem.* **2010**, *45*, 4914.

9. Shi, J. B.; Tang, W. J.; Li, R.; Liu, X. H. *Eur. J. Med. Chem.* **2015**, *90*, 889.

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

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

12. Ouyang, G.; 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.

13. 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.

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

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

16. Tan, C. X.; Shi, Y. X.; Weng, J. Q.; Liu, X. H.; Zhao, W. G.; Li, B. J. *J. Heterocyclic Chem.* **2014**, *51*, 690.

17. Wang, H.; Yang, Z.; Fan, Z.; Wu, Q.; Zhang, Y.; Mi, N.; Wang, S.; Zhang, Z.; Song, H.; Liu, F. *J. Agric. Food Chem.* **2010**, *59*, 628.

18. Zhao, W. G.; Wang, J. G.; Li, Z. M.; Yang, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6107.

19. Fan, Z.; Yang, Z.; Zhang, H.; Mi, N.; Wang, H.; Cai, F.; Zuo, X.; Zhang, Q.; Song, H. *J. Agric. Food Chem.* **2010**, *58*, 2630.

20. Zheng, Q.; Mi, N.; Fan, Z.; Zuo, X.; Zhang, H.; Wang, H.; Yang, Z. *J. Agric. Food Chem.* **2010**, *58*, 7846.

21. Xu, W. M.; Li, S. Z.; He, M., Yang, S.; Li, X. Y.; Li, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5821.

22. Hayat, F.; Salahuddin, A.; Zargan, J.; Azam, A. *Eur. J. Med. Chem.* **2010**, *45*, 6127.

23. Wu, M.; Sun, Q.; Yang, C.; Chen, D.; Ding, J.; Chen, Y.; Lin, L.; Xie, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 869.

24. Fan, Z.; Shi, Z. G.; Zhang, H. K.; Liu, X. F.; Bao, L. L.; Ma, L.; Zuo, X.; Zheng, Q. X.; Mi, N. *J. Agric. Food Chem.* **2009**, *57*, 4279.

25. Wang, T. T.; Bing, G. F.; Zhang, X.; Qin, Z. F.; Yu, H. B.; Qin, X.; Dai, H.; Fang, J. X. *Arkivoc* **2010**, *2*, 330.

26. Dai, H.; Chen, J.; Li, H.; Dai, B. J.; He, H. B.; Fang, Y.; Shi, Y. J. *Molecules* **2016**, *21*, 276.

27. Dai, H.; Shi, Y. J.; He, H. B.; Li, Y.; Wang, S. L.; Li, G.; Li, Y.; Fang, Y. *C. N. Patent 104151308A*, **2014**.

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

29. 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.

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

31. Ling, Y.; Wang, Z. Q.; Zhu, H. Y.; Wang, X. M.; Zhang, W.; Wang, X. Y.; Chen, L.; Huang, Z. J.; Zhang, Y. H. *Bioorg. Med. Chem.* **2014**, *22*, 374.

Graphical abstract

The present work reported that novel pyrazole oximes containing a 1,2,3-thiadiazole moiety displayed good antitumor activity beyond satisfactory insecticidal and acaricidal activities.