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Natural products-based pesticides: Design, synthesis and pesticidal activities of novel fraxinellone derivatives containing *N*-phenylpyrazole moiety

Ruige Yang[a,b,1], Ting Xu[a,1], Jiangping Fan[a], Qian Zhang[a], Ming Ding[a], Mengxing Huang[a], Li Deng[a], Yuchao Lu[c,*], Yong Guo[a,*]

[a] School of Pharmaceutical Sciences, Zhengzhou University, Henan Province, No. 100, KeXue Avenue, Zhengzhou, 450001, PR China
[b] Research Institute of Pesticidal Design & Synthesis, College of Chemistry & Pharmacy, Northwest A&F University, Yangling, 712100, Shaanxi Province, PR China
[c] College of Science and Technology, Hebei Agricultural University, Huanghua, 061100, PR China

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ABSTRACT

Fraxinellone, a degraded limonoid, has been mainly isolated from some renewable plants in Meliaceae and Rutaceae. In a continuous effort to discover new natural products-based pesticides, two series of fraxinellone derivatives containing *N*-phenylpyrazole moiety were designed, synthesized and evaluated for their pesticidal activities against *Mythimna separata* Walker and *Plutella xylostella* Linnaeus. Two structures of compounds **7g** and **8k** were unambiguously determined by X-ray diffraction further. The bioassay showed that over half of the target compounds exhibited better insecticidal activity against *M. separata* than the precursor fraxinellone. Among all the target compounds, the compounds **7g–i** and **8g–j** exhibited more potent insecticidal activity than toosendanin, a commercial botanical pesticide. Furthermore, the compound **8g** displayed more promising larvicidal activity with the LC_{50} value of 0.31 μmol mL^{-1} than the toosendanin against *P. xylostella*. The structure–activity relationship (SAR) revealed that introduction of polyhalogenated phenylpyrazole ring on furyl-ring of fraxinellone could lead more potent compounds both against *M. separata* and *P. xylostella* than that of monohalogenated phenylpyrazole ring or electron-donating groups substituted phenylpyrazole ring.

1. Introduction

Mythimna separata Walker and *Plutella xylostella* Linnaeus both belonging to lepidopteran insect pests, are two typical crop-threatening insect pests. Their larvae can cause great damage to many cereal and crucifer crops such as wheat, rice, maize, cabbage and radish during seasonal outbreaks of their larvae (Sharma et al., 2002; Feng et al., 2014; Sun et al., 2012; Duan et al., 2017; Etebari et al., 2015). Even now, many synthetic chemical pesticides such as organophosphates and organochlorine pesticides have been used to control insect pests, ensure the crop productivity and play a key role in agriculture with their characteristics of quick-acting, low price and broad spectrum. However, the repeated use of these conventional agrochemicals to control lepidopteran insect pests has resulted in pest resistance, pesticide residue and also other side effects on human health (Köhler and Triebskorn, 2013; Heckel, 2012; Lamichhane, 2017). Thus the search for new promising alternatives to effectively and selectively control insect pests has recently received great attention in agriculture field.

Nowadays, many researchers have paid much attention to the traditional folk practices prevalent among peasants and information from classical literature regarding the use of natural products for crop protection (Sparks et al., 2017; Cantrell et al., 2012). Toosendanin (Fig. 1), a limonoid, mainly isolated from *Melia azedarach* and *Melia toosendan*, has been used as a commercial botanical pesticide with low toxicity to control lepidopteran insect pests (Akhtar et al., 2008; Sengottayan, 2013). Fraxinellone **1** (Fig. 1), bearing the furan ring portion and the tetrahydroisobenzofuranone unit, similar to C, D-ring present in limonoids skeleton, is a degraded limonoid isolated from many renewable plants such as *Melia azedarach*, *Azadirachta indica* and *Fagaropsis glabra* (D'Ambrosio and Guerriero, 2002; Ekong et al., 1969; Boustie et al., 1990), and exhibits interesting pesticidal activities according to the previously reported literature (Liu et al., 2008; Lü et al., 2010; Okamura et al., 1997). Fraxinellone **1** also displays low mammalian toxicity. Pioneering work was done by Woo and colleagues (Woo et al., 1987), who reported that the acute oral toxicity (LD_{50}) of fraxinellone was 430 mg kg^{-1} to male mice. In our previous reports, fraxinellone was modified at its furyl-ring, and some halogenated or acylated frxinellone derivatives exhibited higher insecticidal activity

* Corresponding authors.
E-mail addresses: luyuchao_2006@126.com (Y. Lu), guoyong_122@zzu.edu.cn (Y. Guo).
[1] R. Yang and T. Xu contributed equally to this work.

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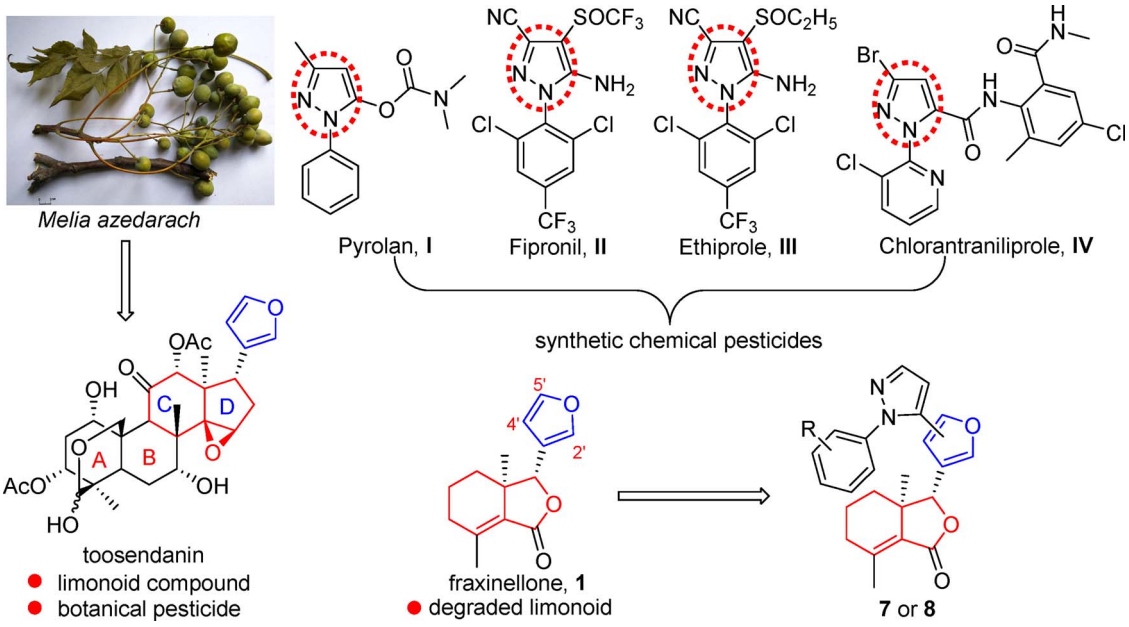

Fig. 1. Design of the target compounds (**7** and **8**).

Table 1
Insecticidal activity of compounds **1**, **4**, **5**, **7a–k** and **8a–k** against *M. separata* fed on leaf discs treated at a concentration of 1 mg mL^{-1} using leaf dip method.

Compound	R	Corrected mortality rate (% ± SD)[a]		
		10 days	20 days	33 days
1	/	13.3(± 3.3)	26.7(± 3.3)	48.3(± 0)
4	/	26.7(± 3.3)	43.3(± 3.3)	58.6(± 0)
5	/	30.0(± 0)	46.7(± 3.3)	62.1(± 3.3)
7a	4-F	20.0(± 5.8)	40.0(± 5.8)	51.7(± 3.3)
7b	4-Cl	23.3(± 3.3)	40.0(± 5.8)	48.3(± 0)
7c	4-Br	16.7(± 3.3)	30.0(± 5.8)	41.4(± 3.3)
7d	4-CH_3	13.3(± 3.3)	33.3(± 3.3)	41.4(± 3.3)
7e	4-CN	20.0(± 5.8)	33.3(± 5.8)	41.4(± 3.3)
7f	4-$CH(CH_3)_2$	13.3(± 3.3)	30.0(± 0)	41.4(± 3.3)
7g	2-F, 4-Br	33.3(± 3.3)	53.3(± 3.3)	72.4(± 3.3)
7h	2-Cl, 4-F	36.7(± 3.3)	53.3(± 3.3)	75.9(± 3.3)
7i	2-Cl, 4-Cl	33.3(± 3.3)	50.0(± 5.8)	69.0(± 0)
7j	2-Cl, 5-F	26.7(± 3.3)	46.7(± 3.3)	55.2(± 3.3)
7k	2-CH_3, 4-CH_3	16.7(± 3.3)	33.3(± 3.3)	48.3(± 5.8)
8a	4-F	20.0(± 0)	43.3(± 3.3)	51.7(± 3.3)
8b	4-Cl	26.7(± 3.3)	40.0(± 0)	51.7(± 3.3)
8c	4-Br	16.7(± 3.3)	40.0(± 5.8)	48.3(± 0)
8d	4-CH_3	20.0(± 5.8)	36.7(± 6.7)	44.8(± 3.3)
8e	4-CN	20.0(± 5.8)	40.0(± 5.8)	51.7(± 6.7)
8f	4-$CH(CH_3)_2$	16.7(± 3.3)	40.0(± 5.8)	48.3(± 0)
8g	2-F, 4-Br	36.7(± 3.3)	60.0(± 0)	75.9(± 3.3)
8h	2-Cl, 4-F	33.3(± 3.3)	60.0(± 5.8)	82.8(± 3.3)
8i	2-Cl, 4-Cl	26.7(± 3.3)	53.3(± 3.3)	69.0(± 0)
8j	2-Cl, 5-F	26.7(± 3.3)	40.0(± 0)	58.6(± 0)
8k	2-CH_3, 4-CH_3	16.7(± 3.3)	36.7(± 3.3)	48.3(± 5.8)
toosendanin	/	16.7(± 3.3)	36.7(± 3.3)	55.2(± 3.3)
blank control	/	0(± 0)	0(± 0)	3.3(± 3.3)

[a] Values are means of three replicate.

Table 2
Larvicidal activity of compounds **1**, **4**, **5**, **7a–k** and **8a–k** against *P. xylostella* fed on leaf discs treated at a concentration of 250 μg mL^{-1}.

Compound	R	Corrected mortality rate (% ± SD)[a]
		72 h
1	/	26.7(± 3.3)
4	/	33.3(± 3.3)
5	/	43.3(± 3.3)
7a	4-F	36.7(± 3.3)
7b	4-Cl	36.7(± 6.7)
7c	4-Br	36.7(± 3.3)
7d	4-CH_3	20.0(± 0)
7e	4-CN	40.0(± 5.8)
7f	4-$CH(CH_3)_2$	20.0(± 0)
7g	2-F, 4-Br	60.0(± 5.8)
7h	2-Cl, 4-F	56.7(± 3.3)
7i	2-Cl, 4-Cl	46.7(± 3.3)
7j	2-Cl, 5-F	30.0(± 5.8)
7k	2-CH_3, 4-CH_3	20.0(± 5.8)
8a	4-F	26.7(± 3.3)
8b	4-Cl	33.3(± 3.3)
8c	4-Br	23.3(± 3.3)
8d	4-CH_3	20.0(± 5.8)
8e	4-CN	30.0(± 0)
8f	4-$CH(CH_3)_2$	23.3(± 3.3)
8g	2-F, 4-Br	63.3(± 3.3)
8h	2-Cl, 4-F	66.7(± 3.3)
8i	2-Cl, 4-Cl	46.7(± 3.3)
8j	2-Cl, 5-F	50.0(± 5.8)
8k	2-CH_3, 4-CH_3	23.3(± 3.3)
toosendanin	/	50.0(± 0)
blank control	/	0(± 0)

[a] Values are means of three replicate.

than toosendanin against *M. separata* (Guo et al., 2016a; Yang et al., 2017). In addition, to the best of our knowledge, little attention has been paid to the introduction of *N*-heterocycle on the furyl-ring of fraxinellone. Pyrazole ring is a highly efficient pharmacophore that is both widely employed in drug and pesticide design. It displays broad spectrum of biological activities, including anticancer, antibacterial, herbicidal, insecticidal, acaricidal activities, *etc* (Khan et al., 2016; Dai et al., 2016; Song et al., 2012). For example, Pyrolan, Fipronil, Ethiprole and Chloraniliprole (Fig. 1, **I–IV**) are representative pyrazole pesticides with great insecticidal activities in the market today (Caboni et al., 2003; Wu et al., 2012). Given the importance of pyrazole scaffolds, and in continuation of our program aimed at the discovery and development of natural product-based pesticides, we sought to design and synthesize some novel 2′ and 5′-*N*-phenylpyrazole fraxinellone derivatives *via* the substructure combination. Finally, we have successfully introduced the *N*-phenylpyrazole moiety on furyl-ring of compound **1** and obtained two series of fraxinellone derivatives containing *N*-phenylpyrazole moiety. The pesticidal activities of these