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Regioselective synthesis of fraxinellone-based hydrazone derivatives as insecticidal agents

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ABSTRACT

In continuation of our program aimed at the discovery and development of natural products-based insecticidal agents, twenty-three new fraxinellone-based hydrazone derivatives were smoothly prepared from fraxinellone via regioselectively allylic oxidation in the presence of selenium dioxide or chromium trioxide under microwave irradiation and subsequent condensation with hydrazides or hydrazines. Their insecticidal activity was evaluated against the pre-third-instar larvae of *Mythimna separata* Walker in vivo. Especially compounds **6d** and **7a** displayed the most pronounced insecticidal activity compared with toosendanin, a commercial botanical insecticide derived from *Melia azedarach*.

Although the routine use of a wide variety of synthetic chemical insecticides in agriculture has now become an accepted practice, the increasing application of those agrochemicals over the years has resulted in the development of resistance in insect pest populations and environmental problems. Development of new effective, selective and safe pesticides, therefore, is highly desirable. Due to plant secondary metabolites resulting from the interaction between plants and environment (life and non-life) during the long period of evolution in plants, consequently, the discovery of new insecticidal compounds from plant secondary metabolites, followed by using them as the lead-compounds for further structural modifications has recently been one of the important procedures for research and development of new pesticides.[1–3]

Fraxinellone (**1**, Fig. 1), a naturally occurring degraded limonoid, isolated from *Dictamnus albus*,[4] *Dictamnus dasycarpus*[5] and *Melia azedarach*,[6] has been found many interesting activities in the field of medicinal chemistry such as antifertility activity,[7] vascular relaxing activity,[8] anti-inflammatory activity,[9] and treating T-cell-mediated liver disorders.[10] Additionally, compound **1** also exhibited the insecticidal activity.[11–14] Although total synthesis of compound **1** has been reported,[15–19] to the best of our knowledge, little attention has been paid to structural modifications of **1** as insecticidal agents. On the other hand, hydrazone fragments have recently received much attention due to their key role in medically important species, such as those displaying antifungal and antimicrobial activities,[20,21] and cyclooxygenase (COX) inhibitors.[22] Based upon the above-mentioned interesting results, and in continuation of our program aimed at the discovery and development of natural products-based insecticidal agents,[3,23–26] herein we designed and prepared a series of fraxinellone-based hydrazone derivatives as insecticidal agents.

Two key intermediates, 3-formylfraxinellone (**2**) and fraxinellonone (**3**), were firstly synthesized from compound **1** by regioselectively allylic oxidation under microwave irradiation.[27] As shown in Scheme 1, in the presence of selenium dioxide (SeO_2, 2 equiv) at 110 °C with a microwave power of 150 W for 2.5 h, compound **2** was obtained as a major product in a 27% yield from **1**, and the yields of byproducts such as **3**, 4β-hydroxyfraxinellone (**4**), and 3-hydroxymethylfraxinellone (**5**) were <7%, 5%, and 3%, respectively. On the contrary, even if a mixture of compound **1** and SeO_2 (2 equiv) in dioxane in the presence of was refluxed for 24 h, the yield of **2** was only 23%. Based upon the above results, similarly, a mixture of **1**, chromium trioxide (1 equiv), pyridine

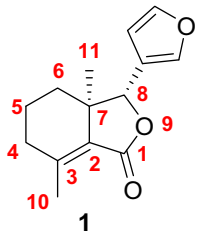

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Figure 1. The chemical structure of fraxinellone (**1**).

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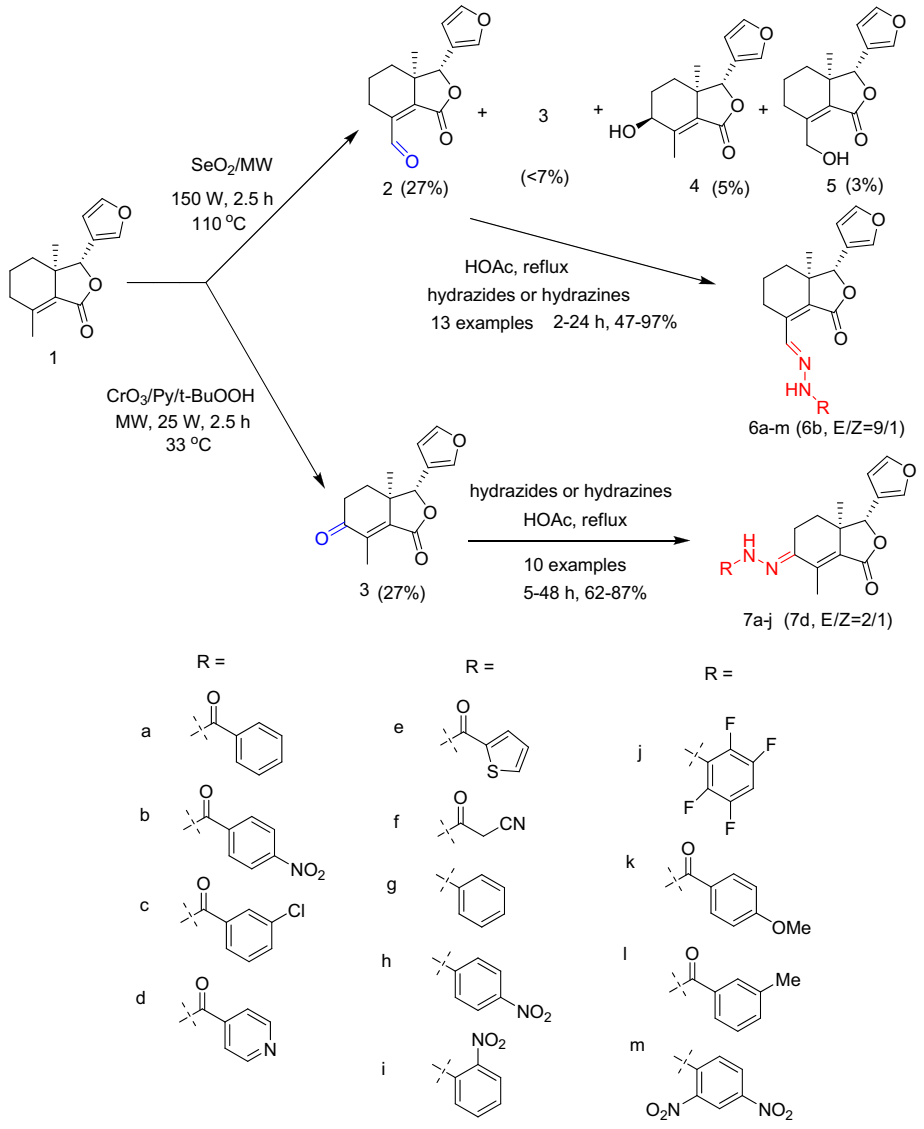

Scheme 1. Synthetic route for the preparation of **6a**–**m** and 7**a**–**j**.

(2 equiv), and 70% aq *t*-BuOOH (10 equiv) in dichloromethane was reacted at 33 °C under microwave irradiation with a power of 25 W for 2.5 h, only compound **3** was regioselectively obtained in a 27% yield. Subsequently, compounds **2** and **3** reacted with hydrazides and hydrazines, respectively, to afford fraxinellone-based hydrazone derivatives **6a–m** and **7a–j**, which were well characterized by ^{1}H NMR, ^{13}C NMR, IR, HRMS and mp (see Supplementary data). Due to the steric hindrance, the substituents on the C=N double bond of all compounds (except *E*/*Z* = 9/1 for **6b**, and *E*/*Z* = 2/1 for **7d**) adopted *E* configuration.[28] To obtain the precise three-dimensional structural information and configuration of **6a–m** and **7a–j**, the single-crystal structures of **3**, **6i**, **7e** and 7**j** were confirmed by X-ray crystallography (Fig. 2–5).[29] The substituents on the C=N double bond of **6i**, **7e** and 7**j** all adopted *E* configuration.

Finally, the insecticidal activity of **1–3**, **6a–m** and **7a–j** was evaluated against the pre-third-instar larvae of *Mythimna separata* Walker in vivo by the leaf-dipping method at the concentration of 1 mg/mL.[25] Toosendanin, a commercial botanical insecticide derived from *Melia azedarach*, was used as the positive control, and leaves treated with acetone alone were used as a blank control group.

As described in Table 1, compared with toosendanin and **1**, compounds **6a**, **6b**, **6d**, **6f**, **6j**, **7a–c** and **7f** exhibited the promising and pronounced insecticidal activity. Especially compounds **6d** and **7a** showed the most pronounced insecticidal activity, and the final mortality rates of **6d** and **7a** were 73.1% and 76.9%, respectively. No significant differences in the insecticidal activity were observed between the hydrazones substituents at the 10- and 4-position of fraxinellone. In general, acyl hydrazones exhibited better insecticidal activity than the corresponding hydrazones. For example, the final mortality rates of acyl hydrazones **6a**, **6b**, **7a** and **7b** were 65.4%, 61.5%, 76.9% and 65.4%, respectively. Whereas the final mortality rates of the corresponding hydrazones **6g**, **6h**, **7g** and **7h** were 53.8%, 38.5%, 46.2% and 53.8%, respectively. When a thiophene group was introduced to acyl hydrazones at the 10- or 4-position of fraxinellone to afford **6e** and **7e**, their insecticidal activity was decreased sharply (e.g., 34.6% for **6e**, and 38.5% for **7e**). Interestingly, introduction of cyanoacetyl hydrazone at the 10- or 4-position of fraxinellone could lead to the potent compounds (e.g., **6f** and **7f**). Hence, the chain of acyl hydrazones should be considered for further structural modifications, and it will be reported in due course.

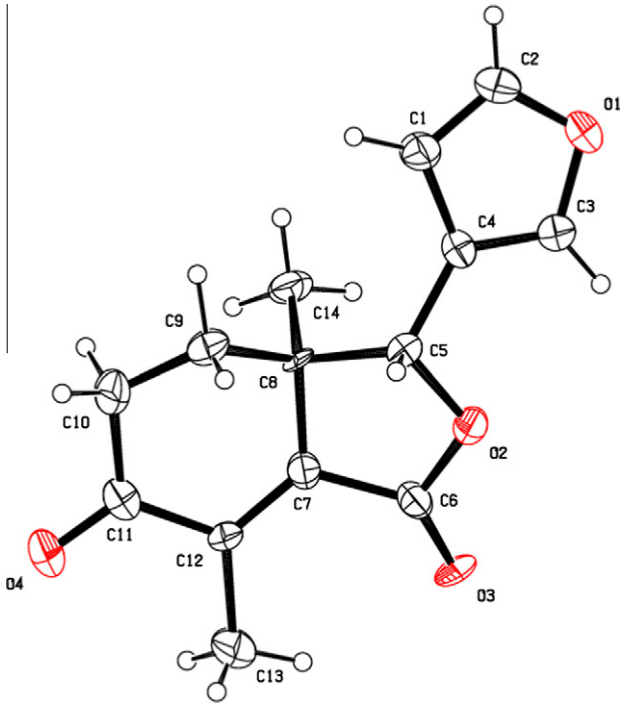

Figure 2. The X-ray crystallography of **3**.

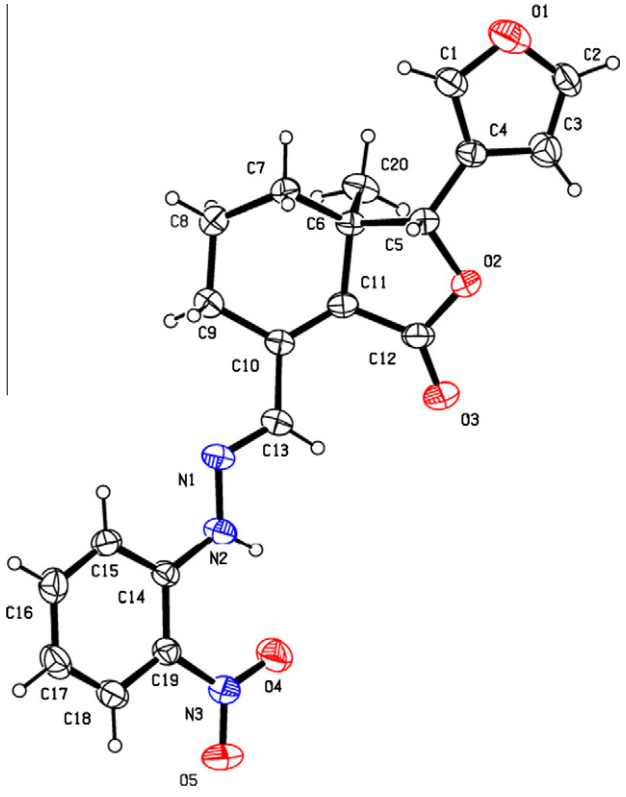

Figure 3. The X-ray crystallography of **6i**.

In summary, a series of novel fraxinellone-based hydrazone derivatives were regioselectively prepared from fraxinellone as insecticidal agents. It was noteworthy that we have reported an

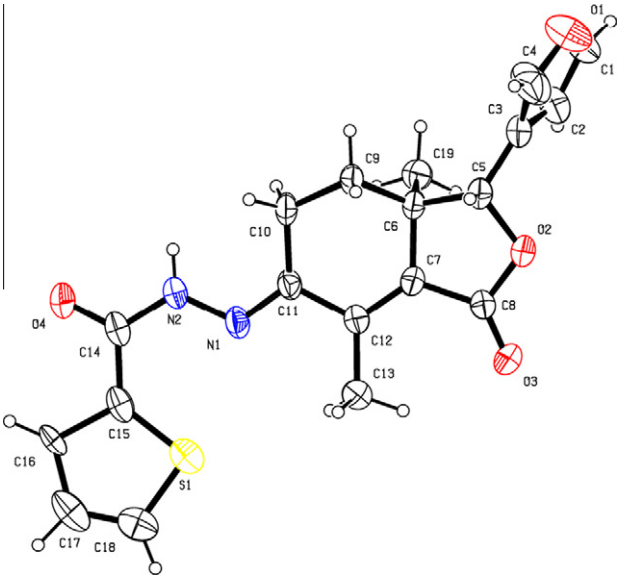

Figure 4. The X-ray crystallography of **7e**.

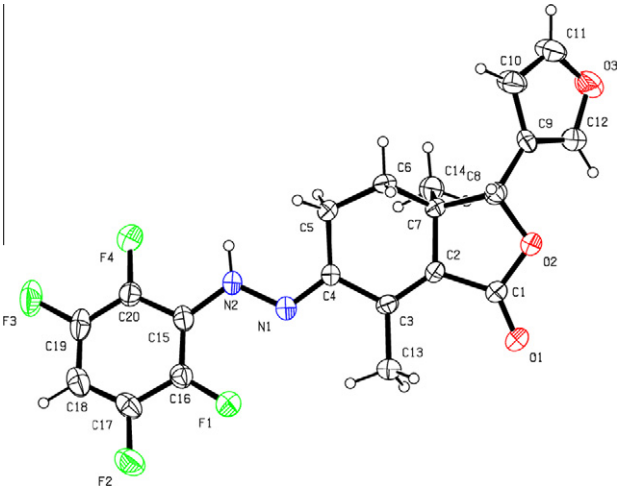

Figure 5. The X-ray crystallography of **7j**.

Table 1
Insecticidal activity of **6a–m** and 7**a–j** at 1 mg/mL against *M. separata*

Compounds	Corrected mortality rate (%)		
	10 d	20 d	35 d
1	41.4 (±9.4)	40.7 (±4.7)	53.8 (±0)
2	17.2 (±8.2)	25.9 (±4.7)	34.6 (±4.7)
3	48.3 (±8.2)	48.1 (±4.7)	57.7 (±4.7)
6a	58.6 (±0)	55.6 (±0)	65.4 (±0)
6b	37.9 (±0)	48.1 (±4.7)	61.5 (±4.7)
6c	44.8 (±4.7)	40.7 (±4.7)	53.8 (±0)
6d	55.2 (±4.7)	66.7 (±8.2)	73.1 (±4.7)
6e	24.1 (±4.7)	29.6 (±9.4)	34.6 (±4.7)
6f	55.2 (±4.7)	66.7 (±0)	69.2 (±4.7)
6g	27.6 (±8.2)	44.4 (±8.2)	53.8 (±0)
6h	20.7 (±4.7)	14.8 (±4.7)	38.5 (±4.7)
6i	13.8 (±4.7)	37.0 (±4.7)	50.0 (±4.7)
6j	37.9 (±0)	40.7 (±9.4)	61.5 (±4.7)
6k	37.9 (±0)	44.4 (±0)	50.0 (±4.7)
6l	41.4 (±4.7)	44.4 (±8.2)	53.8 (±8.2)
6m	31.0 (±12.5)	40.7 (±4.7)	53.8 (±0)

Table 1 (*continued*)

Compounds	Corrected mortality rate (%)		
	10 d	20 d	35 d
7a	58.6 (±0)	63.0 (±4.7)	76.9 (±0)
7b	58.6 (±0)	63.0 (±4.7)	65.4 (±0)
7c	58.6 (±0)	59.3 (±4.7)	69.2 (±4.7)
7d	24.1 (±9.4)	33.3 (±8.2)	50.0 (±4.7)
7e	20.7 (±4.7)	29.6 (±4.7)	38.5 (±4.7)
7f	34.5 (±4.7)	33.3 (±0)	61.5 (±4.7)
7g	10.3 (±9.4)	22.2 (±8.2)	46.2 (±4.7)
7h	34.5 (±4.7)	40.7 (±4.7)	53.8 (±0)
7i	24.1 (±9.4)	33.3 (±0)	46.2 (±4.7)
7j	27.6 (±0)	40.7 (±4.7)	50.0 (±4.7)
Toosendanin	24.1 (±9.4)	33.3 (±0)	53.8 (±0)

efficient route for the regioselectively allylic oxidation of fraxinellone to afford 3-formylfraxinellone and fraxinellonone under microwave irradiation in the presence of selenium dioxide and chromium trioxide, respectively. Especially two compounds of fraxinellone-based hydrazone derivatives displayed the most potent and promising insecticidal activity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.07.058.

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27. Microwave irradiation was performed in a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC, Made in USA).
28. The ratios of *E*/*Z* of **6b** and **7d** were determined by the ^{1}H NMR spectra (see Supplementary data).
29. Crystallographic data (excluding structure factors) for the structures of **3**, **6i**, **7e** and **7j** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 861260, 861285, 861286 and 861287, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (0)1223 336033 or E-mail: deposit@ccdc.cam.ac.uk]