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Natural products-based insecticidal agents 9. Design, semisynthesis and insecticidal activity of 28-acyloxy derivatives of toosendanin against *Mythimna separata* Walker in vivo

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ABSTRACT

In continuation of our program aimed at the discovery and development of natural products-based insecticidal agents, twelve 28-acyloxy derivatives of toosendanin (**2a**–**l**) were semisynthesized and preliminarily evaluated their activity against the pre-third-instar larvae of *Mythimna separata* Walker in vivo at the concentration of 1 mg/mL. Some compounds exhibited the potent insecticidal activity. Especially compounds **2c** and **2j** displayed the more promising insecticidal activity than their natural precursor, toosendanin, a commercial insecticide derived from *Melia azedarach* at 1 mg/mL. In general, it indicated that the butanoyloxy or phenylacryloyloxy moiety at the 28-position of toosendanin was essential for the insecticidal activity.

Although the routine use of a wide variety of synthetic insecticides in agriculture has now become an accepted practice, the application of those agrochemicals over the years has resulted in the development of resistance in insect pest populations and environmental problems. As plant secondary metabolites result from the interaction between plants and environment (life and non-life) during the long period of evolution in plants, therefore, the discovery and development of new insecticidal compounds from plant secondary metabolites, followed by using them as the lead-compounds for further modifications has been one of the important ways for research and development of new pesticides in recent years.[1]

Toosendanin (**1**, Fig. 1), a limonoid, isolated from *Melia azedarach*, has been mainly used as an effective anti-botulinum agent for botulism in the field of medicinal chemistry.[2–5] On the other hand, compound **1** also exhibited the interesting insecticidal activity.[6–9] To the best of our knowledge, however, little attention has been paid to structural modifications of **1** as an insecticidal agent. In continuation of our program aimed at the discovery and development of natural products-based insecticidal agents,[1,10–13] consequently, in this Letter we wanted to design and prepare a series of 28-acyloxy derivatives of toosendanin, by structural modifications on the C-28 position of **1**, as an insecticidal agent.

As shown in Scheme 1, twelve 28-acyloxy derivatives of toosendanin (**2a**–**l**) were successfully prepared in 39–78% yields. In the presence of NaOAc in dried acetone, compound **1** reacted with acetic anhydride or propionic anhydride at reflux to give **2a** or **2b**. Compounds **2c**–**l** were obtained from ordinary esterifications of **1** with carboxylic acids by using of *N*,*N*′-diisopropylcarbodiimide (DIC) as a condensation agent, and a catalytic amount of 4-dimethylaminopyridine (DMAP) at room temperature. The structures of all target compounds were well characterized by ^{1}H NMR, ^{13}C NMR, MS, HR-MS, IR, and mp (see Supplementary data).

To obtain the precise three-dimensional structural information and absolute configuration of **2a**–**l**, the representative single-crystal structure of **2c** was determined by X-ray crystallography (Fig. 2).[14] It clearly suggested that the butanoyloxy group at the C-28 position of toosendanin adopted the *exo*-configuration.

The insecticidal activity of **2a**–**l** against the pre-third-instar larvae of *Mythimna separata* Walker was tested at the concentra-

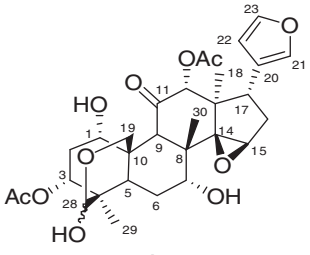

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Figure 1. Chemical structure of toosendanin (**1**).

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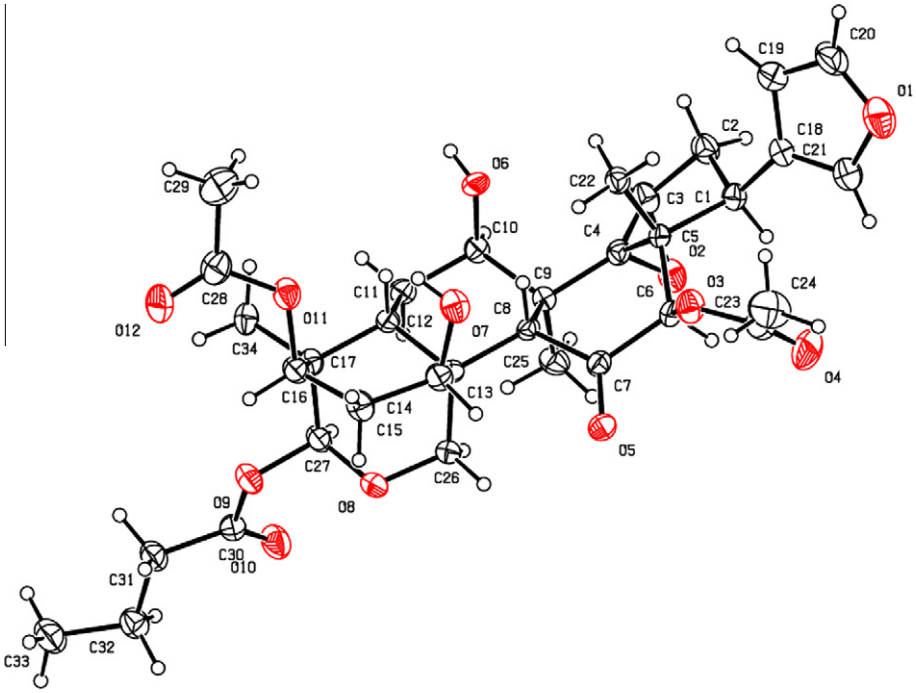
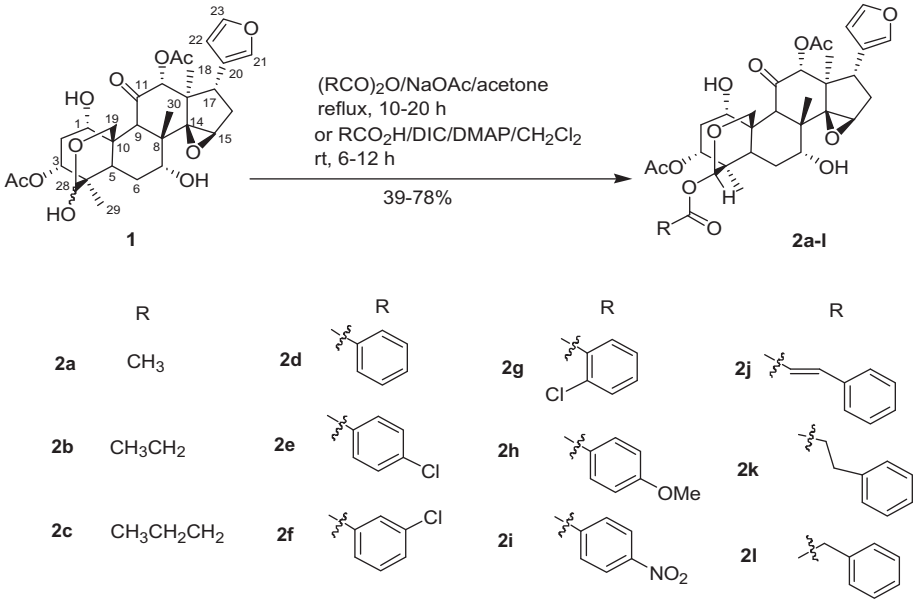


Figure 2. The X-ray crystallography of compound **2c**.



Scheme 1. The synthetic route of 28-acyloxy derivatives of toosendanin (**2a**–**l**).

tion of 1 mg/mL by leaf-dipping method.[10] Compound **1**, a commercially botanical insecticide, was used as a positive control at 1 mg/mL.

The corrected mortality rates of *M. separata* caused by **1** and **2a**–**l** with the advance of time were described in Figure 3. It was observed that the corresponding mortality rates after 35 d were far higher than those after 10 and 20 d. That is, these compounds, in a time-dependent manner, different from those conventional neurotoxic insecticides, such as organophosphates, carbamates, and pyrethroids, exhibited delayed insecticidal activity. For example, the corrected mortality rate of **2j** against *M. separata* after 10 d was 20.7%, after 20 d the corresponding mortality rate was increased to 38.5%, but after 35 d the corresponding mortality rate was rapidly increased to 61.5% (Table 1).

Meanwhile, the symptoms of the tested *M. separata* were characterized by the same way as our previous reports.[10–13] The pupation of the larvae and the adult emergence of *M. separata* were inhibited by these compounds, therefore, the period from the larvae to adulthood of *M. separata* was prolonged as compared with the blank control group. In other words, these compounds showed growth inhibitory effects. Due to feeding too much treated leaves during the first 48 h, some larvae died slowly with the slim and wrinkled bodies during the larval period (Fig. 4). Moreover, many larvae of the treated groups moulted to malformed pupae, which could not reach adulthood and died during the stage of pupation because they were not able to remove their pupal skin (Fig. 5). Malformed moths with imperfect wings were also appeared in the treated groups (Fig. 6).

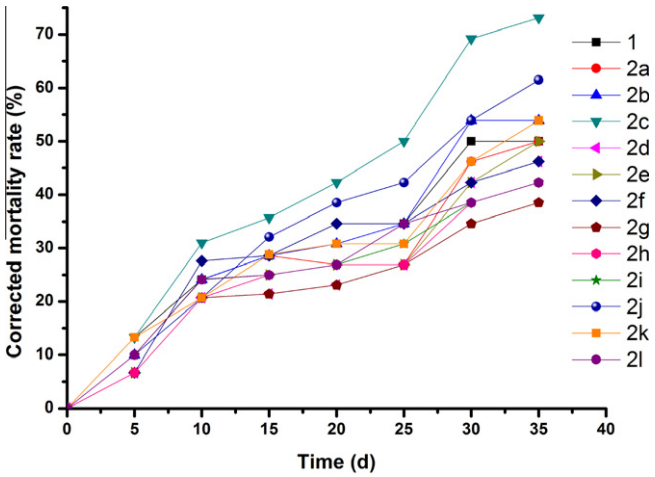


Figure 3. The corrected mortality rates of *M. separata* caused by **2a**–**l** with the increase of time.

Table 1
Insecticidal activity of **2a**–**l** against *M. separata* in vivo at 1 mg/mL

Compound	Corrected mortality rate (%)		
	10 d	20 d	35 d
1	24.1 (±4.7)	30.8 (±0.0)	50.0 (±4.7)
2a	24.1 (±4.7)	26.9 (±4.7)	50.0 (±12.5)
2b	24.1 (±9.4)	30.8 (±8.2)	53.9 (±8.2)
2c	31.0 (±4.7)	42.3 (±8.2)	73.1 (±4.7)
2d	20.7 (±4.7)	23.1 (±4.7)	46.2 (±4.7)
2e	20.7 (±4.7)	26.9 (±4.7)	50.0 (±9.4)
2f	27.6 (±0.0)	34.6 (±4.7)	46.2 (±12.5)
2g	20.7 (±4.7)	23.1 (±4.7)	38.5 (±4.7)
2h	20.7 (±4.7)	26.9 (±4.7)	42.3 (±8.2)
2i	24.2 (±4.7)	26.9 (±4.7)	42.3 (±0.0)
2j	20.7 (±4.7)	38.5 (±9.4)	61.5 (±4.7)
2k	20.7 (±4.7)	30.8 (±0.0)	53.9 (±8.2)
2l	24.1 (±4.7)	26.9 (±4.7)	42.3 (±8.2)

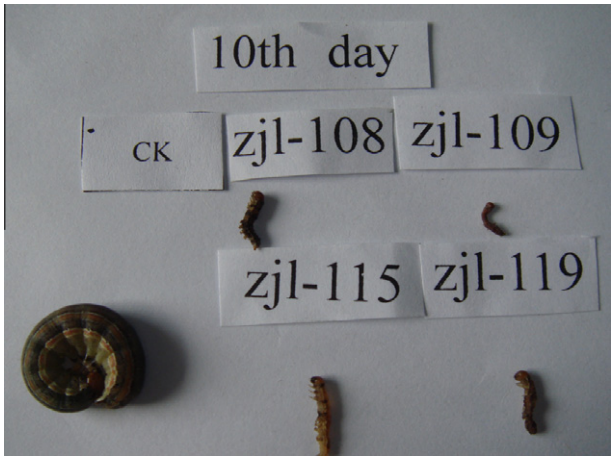


Figure 4. The representative abnormal larvae pictures of **2a** (zjl-108), **2b** (zjl-109), **2e** (zjl-115), and **2g** (zjl-119) during the larval period.

As shown in Table 1, compounds **2c** and **2j** exhibited the more potent insecticidal activity than their natural precursor, toosendanin. Based upon study on the relationship between the chemical structures and the insecticidal activity (SAR) of **2a**–**l**, some interesting results were preliminarily concluded as follows: (1) The proper length of alkyloyloxy group at the 28-position of toosendanin was

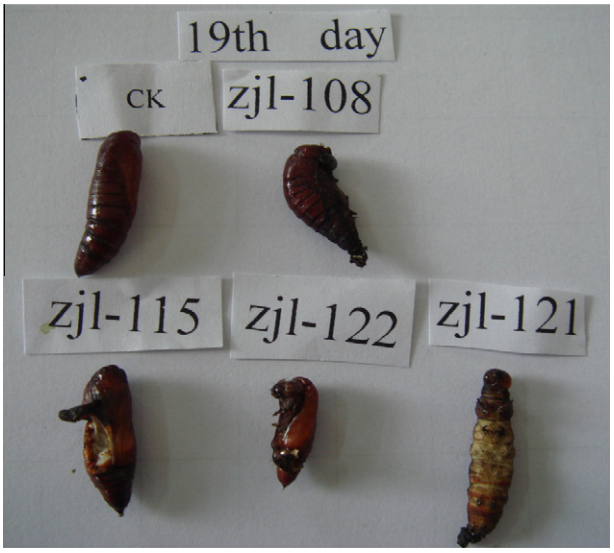


Figure 5. The representative malformed pupae pictures of **2a** (zjl-108), **2c** (zjl-121), **2e** (zjl-115), and **2j** (zjl-122) during the pupation period.

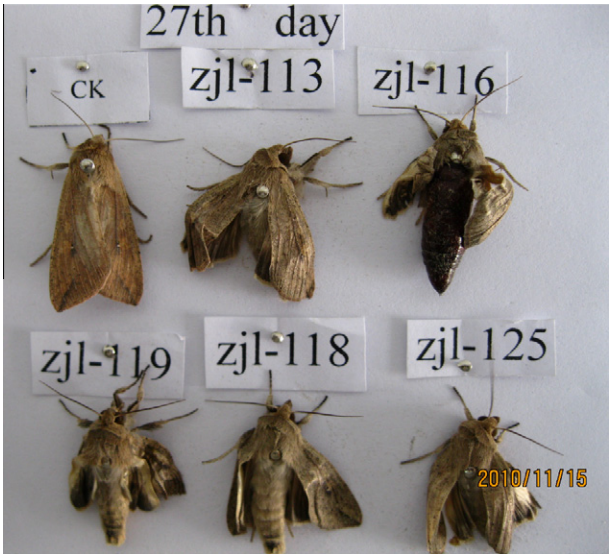


Figure 6. The representative malformed moth pictures of **2d** (zjl-113), **2f** (zjl-116), **2g** (zjl-119), **2i** (zjl-118), and **2k** (zjl-125) during the emergence period.

usually important for their insecticidal activity. For example, the final mortality rates of **2a** and **2b**, which possess the acetoxy and propionyloxy groups, respectively, were 50% and 53.9%, respectively. While introduction of the butanoyloxy group at the 28-position of **1** afforded **2c**, and the corresponding mortality rate of **2c** was sharply increased to 73.1%. (2) In general, the electronic effects of substituents at the 28-position to the insecticidal activity were not very obvious (**2d** vs **2h** vs **2i**). However, the influence of steric effects on the insecticidal activity was observed to some degree. For example, the final mortality rates of **2e** (having 4-Cl), **2f** (having 3-Cl), and **2g** (having 2-Cl) were 50%, 46.2%, and 38.5%, respectively. (3) The insecticidal activity of the phenylalkyloyloxy series (**2j**–**l**) decreased in order phenylacryloyloxy (**2j**) > phenylpropionyloxy (**2k**) > phenylacetoxy (**2l**). It demonstrated that the double bond of the phenylacryloyloxy group was important for the insecticidal activity.

In conclusion, twelve 28-acyloxy derivatives of toosendanin (**2a**–**l**) were semisynthesized and preliminarily evaluated their

activity against the pre-third-instar larvae of *M. separata* in vivo at 1 mg/mL. Especially compounds **2c** and **2j** exhibited the more potent insecticidal activity than their natural precursor. Generally, it suggested that the butanoyloxy or phenylacryloyloxy moiety at the 28-position of toosendanin was essential for the insecticidal activity. The afore-mentioned results will encourage us to further investigate new toosendanin derivatives as insecticidal agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.031.

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14. Crystallographic data (excluding structure factors) for the structure of **2c** in this Letter has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 803606. 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].