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Furan-site transformations of obacunone as potent insecticidal agents

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Abstract

Furan ring is a key pharmacophore for insecticidal activity of limoninoids. To develop natural-product-based insecticidal agents, a series of furan-site transformations (**2**, **3** and **3a−j**) of obacunone were synthesized by selective bromination and following coupling reactions without altering other functional groups. Bioassays indicated that derivatives **3e**, **3f** and **3j** displayed more potent insecticidal activity than obacunone and toosendanin against the instar larvae of *Mythimna separate* Walker. Besides, their structure−activity relationships were discussed.

Keyword: Natural product chemistry

1. Introduction

Mythimna separata Walker (oriental armyworm) is a typical insect pest through crop-destruction [1]. In the past decades of controling agricultural pests, the wanton use of synthetic agrochemicals has resulted in many problems such as pesticide-resistance, and environmental problems [2]. Therefore, development of potential alternatives to efficiently control insect pests is becoming rather desirable [2, 3, 4, 5]. Natural products (NPs) are playing an important role in novel pesticide discovery due to their potential target sites, low toxicity and environment-friendly characteristics [6, 7, 8, 9, 10, 11, 12]. Besides, natural product derivatives (NPDs) often improve their pharmaceutical effects, such as in the new drugs discovery between 1981 and 2014, NPDs is over 5 times than NPs [13]. In the development from NPs to diverse NPDs, semisynthesis with highly selective transformations is an attractive approach.

Furan ring, as a critical pharmacophore, is widely present in many active natural products [14, 15] such as toosendanin (a known natural-product insecticidal agents) [16, 17] and limonin [18] (Fig. 1). Yet, the lack of furan-site chemical handle has limited the furan-site diversity of NPs [19]. Obacunone (**1**, Fig. 1), is another natural limonoid with a furan ring from many species of plants [20, 21, 22, 23, 24] such as Citrus and Dictamnus angustifolius. It has exhibited many activities such as anti-cancer [25, 26, 27, 28], antimalarial [29], and antioxidant activities [30], and also showed insecticidal activities such as the moult inhibiting activity [31] and the anti-feedant activity [32]. Up to now, obacunone has been focused on isolation, and few semisynthetic examples were reported on modifications at C-7 carbonyl group (B-ring) [32, 33, 34, 35].

Recently, we reported the bromination of fraxinellone by *N*-bromosuccinimide (NBS, as a brominating reagent) and Br$_2$ (as a catalyst) or by 1,3-dibromo-5,5-dimethylhy-dantoin (DBDMH, another brominating reagent) and following couplings, and found some furan-site modified derivatives displayed more potent insecticidal activity than toosendanin [36]. In our endeavor aiming at finding

Furan-containing natural products
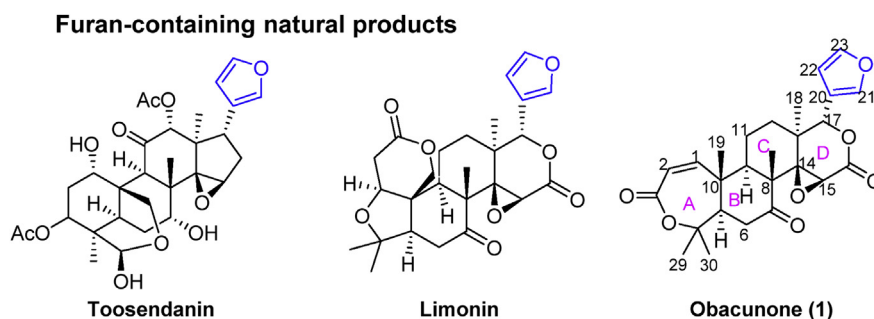
Fig. 1. Furan-containing natural products: toosendanin, limonin and obacunone (**1**) as potent insecticidal agents.

more active natural product-based insecticidal hits [36, 37, 38, 39, 40], herein we prepared a series of furan-site transformed derivatives of obacunone (**1**) by selectively altering furan ring (Fig. 2). Besides, their insecticidal activity were tested against *M. separata* Walker.

2. Results & discussion

As shown in Fig. 3, obacunone (**1**) was used as the starting material and the bromination reaction conditions was firstly optimized. DBDMH was selected to brominate the furan ring due to its advantages of higher bromine content and more stable structure than NBS. The loading amount of DBDMH was investigated. When the reaction was carried out with 1.4 eq DBDMH, dibromination derivative **3** was produced in 60% yield as the sole product. However, treatment with 0.5 eq DBDMH gave the mixture of at least three components containing monobromination **2** (21%), dibromination **3** (<5%) and recovered **1** (21%). When NBS or NBS with catalytic Br_2 was carried out this reaction, no product was obtained (data not shown), which was different from previous studies on fraxinellone [36], indicating that DBDMH is more suitable for the furan-site bromination of obacunone. Consequently, **3** was prepared in gram-scale with 1.4 eq DBDMH in 58% yield in Fig. 3.

With dibromo-obacunone **3** in hand, various alkyl, aryl and alkynyl substituents were appended to the C-21 and C-23 positions in **3** through palladium-catalyzed coupling reactions (Fig. 4). Different aryl or alkyl boronic acid reacting with **3** afforded derivatives **3a-i** by Suzuki-Miyaura coupling reactions in moderate to good yields. Meantimes, alkynyl introduced derivative **3j** was prepared using Sonogashira coupling. As shown in Fig. 4, phenyl and naphthyl boronic acids typically produced moderate yields (**3a** 36%, **3b** 36%) in the Suzuki-Miyaura coupling. In addition, phenyl rings bearing electron-donating substituents produced fair yields (**3d** 56%, **3e** 78%). However, aliphatic substituents derivatives did not showed good yields (**3g** 16%, **3h** 15%, **3i** 19%), perhaps due to electronic effect. Sonogashira coupling reaction with phenylethyne from sp [2]- and sp [3]-hybridized substitutions to alkyne
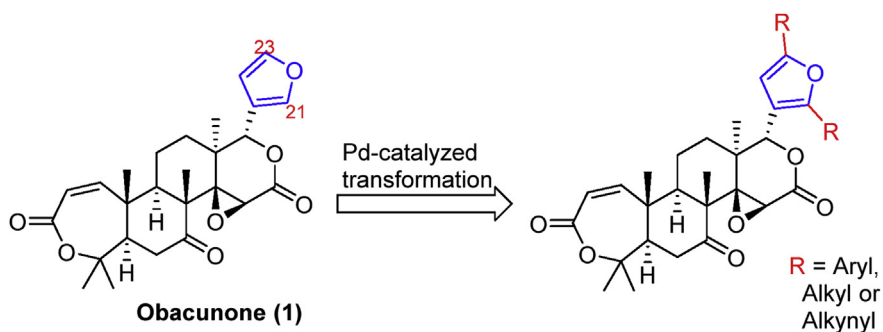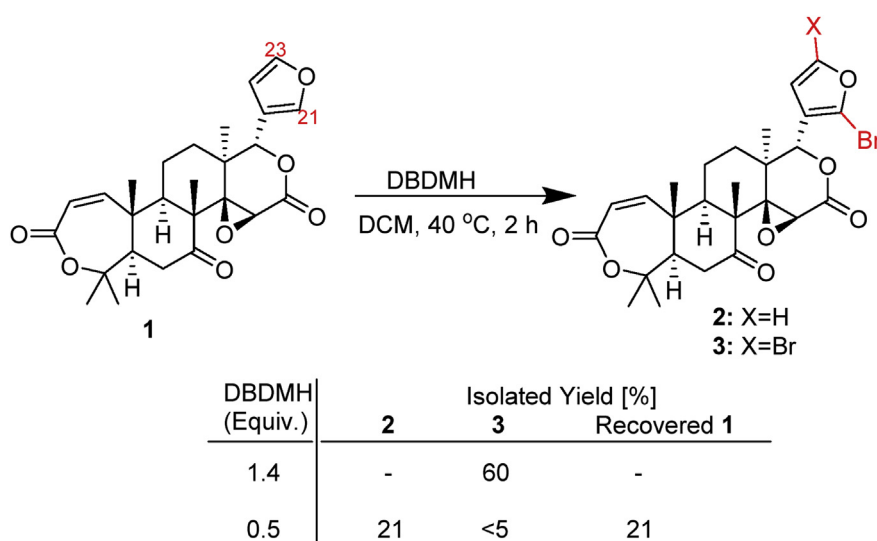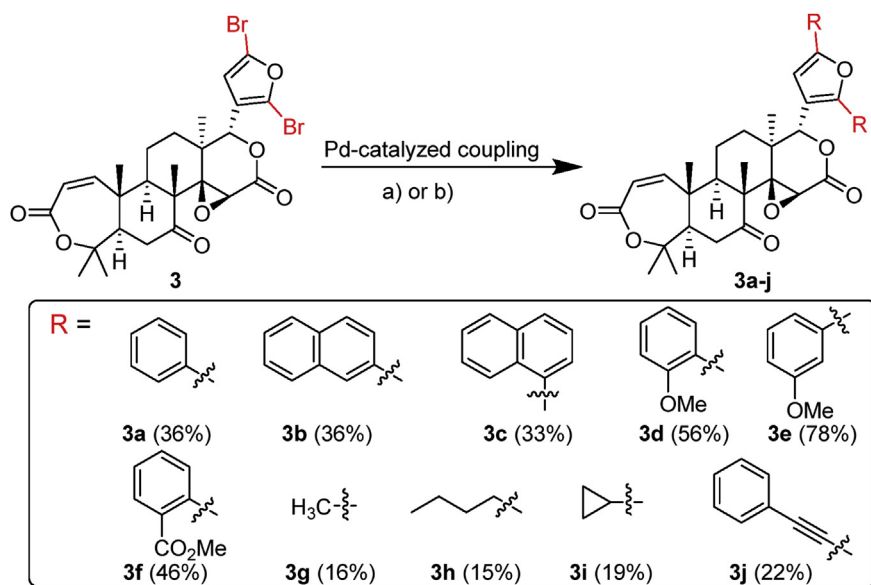

Fig. 2. Palladium-catalyzed transformations of **1**.

DBDMH (Equiv.)	Isolated Yield [%]		
	2	3	Recovered 1
1.4	-	60	-
0.5	21	<5	21

Fig. 3. Investigation of **1** reacting with brominating reagent 1,3-dibromo-5,5-dimethylhydantoin (DBDMH).

3a-i: a) RB(OH)$_2$ (4 equiv), Pd$_2$dba$_3$ (0.04 equiv), XPhos (0.16 equiv), K$_3$PO$_4$ (3 equiv), PhMe, 60°C, 16 h.
3j: b) phenylethyne (4 equiv.), PdCl$_2$(PPh$_3$)$_2$ (0.05 equiv.), CuI (0.1 equiv.), THF/Et$_3$N (1:1), 60°C, 16 h.

Fig. 4. Palladium-catalyzed couplings of **3**.

substitutents gave a transformed derivative **3j** in 22% yield. The structures of all derivatives were determined by optical rotation, NMR and HRMS. Their analytical characterization data and spectra can be found in Supplementary material. On the other hand, various ligands is also under consideration for further investigation.

The insecticidal activity of all compounds was tested against the pre-third-instar larvae of *M. separata* by the leaf-dipping method as the mortality rates at 1 mg/mL [41]. Toosendanin (a commercial natural-product insecticide) was used as a positive control at 1 mg/mL. The corrected mortality rate was outlined in Table 1. All prepared derivatives of obacunone (**2**, **3** and **3a-j**) exhibited the delayed insecticidal activity against *M. separata*. For example, the corrected mortality rates of **3c** against *M. separata* after 10 and 20 days were 8.3% and 8.3%, respectively. However, it was sharply increased to 45.8% after 35 days, which was over 4-fold of that after 10 days. Among all derivatives, **3e**, **3f** and **3j** displayed more potent insecticidal activity than their precursor **1** and toosendanin. The final mortality rates of **3e**, **3f** and **3j** were 45.8%, 50.0% and 45.8%, respectively; whereas the final mortality rates of **1** and toosendanin were 37.5% and 33.3%, respectively. Notably, derivatives with excellent mortality have good teratogenic activity on different stages. During the pupation stage, some malformed and dead pupae were present (Fig. S1), and during the adult emergence stage, some moths have been malformed from eclosion (Fig. S2). The malformed pupae and moths suggested that obacunone derivatives probably affected the insect molting hormone.

Meanwhile, some interesting SAR results were also observed: 1) Comparing mortality rates of **1** and mono- and di-bromination derivatives (**2** and **3**), introductions of

Table 1. Insecticidal activity of all obacunone derivatives against *M. separata* on leaves treated with a concentration of 1 mg/mL.

Compound	Corrected mortality rate [%][a]		
	10 days	20 days	35 days
1	12.5 ± 7.9	29.2 ± 4.2	37.5 ± 3.9
2	12.5 ± 3.2	12.5 ± 3.2	16.7 ± 1.7
3	0.0 ± 0.0	0.0 ± 0.0	8.3 ± 5.7
3a	8.3 ± 3.2	12.5 ± 4.7	25.0 ± 4.2
3b	12.5 ± 1.7	12.5 ± 1.6	33.3 ± 5.7
3c	12.5 ± 0.0	16.7 ± 3.3	29.2 ± 6.1
3d	8.3 ± 2.0	12.5 ± 1.4	29.2 ± 4.2
3e	16.7 ± 3.9	25.1 ± 3.3	45.8 ± 4.2
3f	25.0 ± 1.6	29.2 ± 1.7	50.0 ± 5.7
3g	8.3 ± 3.2	8.3 ± 3.2	33.3 ± 1.7
3h	8.3 ± 1.6	8.3 ± 1.6	41.7 ± 5.7
3i	0.0 ± 0.0	0.0 ± 0.0	4.2 ± 3.4
3j	8.3 ± 4.2	8.3 ± 4.2	45.8 ± 6.1
Toosendanin	29.2 ± 2.0	29.2 ± 1.7	33.3 ± 5.7
Blank control	0 ± 0	0 ± 0	0 ± 0

[a] All data (mean ± SD) are the average of four independent groups (six larvae per group).

one or two bromine atoms reduced the insecticidal activity, different with bromo-fraxinellone which showed stronger activity than fraxinellone; 2) **3e**, **3f**, and **3j** displayed more potent insecticidal activity than toosendanin, indicating that aromatic chain with substituents may lead to an improved level of insecticidal activity; 3) **3f** displayed the strongest insecticidal activity at different test days (10, 20 and 35 days), indicating aromatic chain with electron-withdrawing group in phenyl can improve insecticidal activity; 4) Furthermore, comparing mortality rates of derivatives of obacunone and fraxinellone with the same furan-substituted moieties in Table S1, insert of two phenyl or n-C_4H_9 in the furan site of obacunone (**1**) and fraxinellone gave little influence of the insecticidal activity, yet showed remarkable decreased activity for the reduced fraxinellone, implying the phenyl without substituents and n-C_4H_9 may be not good introduce groups for insecticidal activity.

3. Conclusion

In conclusion, we prepared a series of furan-site transformed derivatives of obacunone (**1**) through selective bromination and Pd-catalyzed couplings. Using the brominating agent DBDMH, the dibromobacunone **3** was obtained in good yield without influencing other groups. Consequently, a series of derivatives were coupled with different alkyl, aryl and alkynyl substituents by Suzuki-Miyaura or Sonogashira coupling reactions, which enriched the diversity of obacunone. Bioassay test showed that derivatives **3e**, **3f** and **3j** had higher insecticidal activity against *M. separate* than parental counterpart **1** and toosendanin. This study provides a highly amenable modification for the synthesis of furan-containing NPs that could be used as biological probes or the lead compounds for further chemical modifications.

4. Experimental

4.1. General information

All NMR spectra were recorded on a 500 MHz Bruker NMR spectrometer in $CDCl_3$ with TMS as internal standard for ^{1}H NMR and solvent signals as internal standard for ^{13}C NMR. Chemical shift values are mentioned in δ (ppm) and coupling constants (*J*) are given in Hz. HR-ESI-MS spectra were recorded on an ESI-Thermo Fisher LTQ Fleet instrument spectrometer or AB Sciex 5600 Triple TOF mass spectrometer. Column chromatography (CC) was performed over silica gel (200−300 mesh, Qingdao Marine Chemical Ltd.). All reactions were monitored by thin-layer chromatography carried out on 2 cm × 5 cm precoated silica gel GF_{254} plates of thickness of 0.25 mm (Qingdao Marine Chemical Group, Co.) with UV light (254 nm and 365 nm), and were visualized using 5% phosphomolybdic acid followed by heating. All commercially available solvents and reagents were freshly purified and dried by standard techniques prior to use.

4.2. Synthesis of 2 and 3

A Schlenk tube was charged with obacunone (**1**) (1.00 g, 2.20 mmol) and DBDMH (880.59 mg, 3.08 mmol, 1.4 equiv.), and the second tube was charged with obacunone (**1**) (1.00 g, 2.20 mmol) and DBDMH (314.53 mg, 1.10 mmol, 0.5 equiv.). Then the DCM (100 mL) was added to each tube. The reaction mixture was stirred at 25 °C and kept in the dark for 2 h. After the reaction was completed, the mixture was subjected to silica gel flash chromatography directly, using petroleum ether/ acetone (5: 1, V/V), gave **2** and **3** in yields as listed in Fig. 3.

4.3. Synthesis of 3a-i

The typical Suzuki-Miyaura couplings were utilized with reference [42]. An oven-dried Schlenk tube was charged with **3** (40.4 mg, 0.129 mmol), Pd_2dba_3 (4.7 mg, 0.0051 mmol), SPhos (9.8 mg, 0.020 mmol), boronic acid (0.516 mmol) and K_3PO_4 (82.2 mg, 0.387 mmol). The tube was evacuated and flushed with argon 5 times before adding toluene (5 mL). After stirring at room temperature for 5 min, the reaction mixture was heated to 60 °C for 16 h. Then the reaction was cooled to room temperature, diluted with EtOAc (3 mL) and filtered through a thin pad of silica gel. Solvent was evaporated under reduced pressure. Flash chromatography of the residue over silica gel (1.5 × 30 cm), using petroleum ether/acetone (3: 1∼8: 1, V/V), gave **3a-i** in yields as listed in Fig. 4.

4.4. Synthesis of 3j

The typical Sonogashira couplings were utilized with reference [43]. An oven-dried Schlenk tube was charged with **3** (40.4 mg, 0.129 mmol), $PdCl_2(PPh_3)_2$ (4.5 mg, 0.006 mmol) and CuI (2.5 mg, 0.013 mmol). The tube was evacuated and flushed with argon 5 times before adding toluene (3 mL) and $THF-Et_3N$ (1:1, 2 mL). After stirring at room temperature for 5 min, phenylethyne (516 mmol) was added. Then the reaction mixture was heated to 80 °C for 16 h. When the reaction was completed, the reaction mixture was cooled to room temperature and filtered through a thin pad of silica gel, rinsing with EtOAc (70 mL). Then the filtrate was rinsed with 1 N HCl (∼20 mL) and brine (∼20 mL). The organic layer was dried over $NaSO_4$, concentrated in vacuo. Flash chromatography of the residue over silica gel (1.5 × 30 cm), using petroleum ether/acetone (5:1), gave **3j** in yield as listed in Fig. 4.

4.5. Biological assay

The insecticidal activity of **1-3** and **3a-j** was tested as the mortality rate values by using the leaf-dipping method against the pre-third-instar larvae of *Mythimna separate* using the reported procedure [36]. For each sample, a total of 24 pre-third-instar larvae (6 larvae per group) were used. Each treatment was performed four times.

Acetone solutions of **1-3** and **3a-j** and toosendanin (positive control) were prepared at 1 mg/mL. Fresh wheat leaf discs (1×1 cm) were dipped into the corresponding solution for 3 s, then taken out and dried. Leaf discs treated with acetone alone were used as a blank control group. Several pieces of treated leaf discs were kept in each 6 well plate which was then placed in a conditioned room ($25 \pm 2\ °C$, $65-80\%$ relative humidity (RH), 12 h/12 h (light/dark)). Once the treated leaves were consumed, the corresponding ones were added to the dish. After 48 h, untreated fresh leaves were added to the all dish until the adult emergence. At the same time, the corrected mortality rate of the tested compounds against third-instar larvae of *M. separata* was calculated by the following formula:

$$\text{corrected mortality rate } (\%) = (T - C\ )/(100\% - C) \times 100\%$$

(T=test compound groups, C=blank control group)

Declarations

Author contribution statement

Jiang-Jiang Tang: Conceived and designed the experiments; Wrote the paper.

Qing-Hao Cao, Qing-Miao Dong: Performed the experiments.

Ping Xiang: Analyzed and interpreted the data.

Xiao-Jun Yang, Hongjin Bai: Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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