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# Natural products-based insecticidal agents 20. Design, synthesis and insecticidal activity of novel honokiol/magnolol azo derivatives

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ABSTRACT

Honokiol and magnolol are small-molecule polyphenols isolated from the barks of *Magnolia officinalis*. To discover novel natural-product-based pesticidal agents, a series of honokiol/magnolol azo derivatives were prepared by structural modification of honokiol or magnolol. Their insecticidal activity was evaluated at 1 mg/mL against the pre-third-instar larvae of oriental armyworm (*Mythimna separata* Walker), a typical lepidopteran pest. Among all derivatives, **5m** and **6k** exhibited more promising insecticidal activity with the final mortality rates greater than 60%, when compared with their precursors (honokiol and magnolol) and the positive control, toosendanin.



## 1. Introduction

Lepidoptera is one of the most widely recognizable insect orders in the world, comprising an estimated 174,250 species in 126 families and 46 superfamilies (Capinera, 2008). The outbreaks of their larvae could result in a widespread and complete crop loss in agriculture (Wang et al., 2006). Therefore, many kinds of synthetic agrochemicals have been used to control the larvae of lepidopteran pests in agriculture during the past decades. On the other hand, repeat application of those synthetic agrochemicals has led to the development of resistance in lepidopteran pest populations and environmental problems (Sun et al., 2012; Velez et al., 2013; Showler et al., 2013; Guillette and Iguchi, 2012). Conversely, new insecticides produced from plant secondary metabolites, which originated from the interaction between the plants and the environment (life and non-life) during the long period of plants evolution, may lead to less or slower resistance development and lower environmental pollution (Xu, 2013). Consequently, research and development of natural-product-based insecticidal agents as the potential alternatives for controlling insect pests has nowadays become more and more attractive in the agricultural field (Chu et al., 2011; Lin et al., 2012; Sousa et al., 2013; Diao et al., 2013; Wukirsari et al., 2013; Zhang et al., 2013; Wu et al., 2013).

Honokiol (**1**, Fig. 1) and magnolol (**2**, Fig. 1), are small-molecule polyphenols isolated from the barks of *Magnolia officinalis*, which were widely used in traditional Chinese and Japanese medicines (Song and Fischer, 1999). Meanwhile, compounds **1** and **2** exhibited a variety of biological properties, such as antioxidative activity (Li et al., 2003), antimicrobial activity (Kim et al., 2010), anticancer activity (Battle et al., 2005), antiviral activity (Amblard et al., 2006), anti-inflammatory activity (Lin et al., 2013), anxiolytic activity (Kuribara et al., 2000), and antiplatelet activity (Shih and Chou, 2012). Meanwhile, the azo moiety was found in some molecules, which displayed various medicinal and pesticidal activities (Fondjo et al., 2013; Romero-Canelon et al., 2013; Takahashi et al., 2000; Xu and Zeng, 2010). To the best of our knowledge, little attention has been paid to structural modifications of **1** and **2** as insecticidal agents. As part of our ongoing search for new potential natural-product-based insecticidal agents to control the lepidopteran pests (Zhi et al., 2013; Che et al., 2013), herein we synthesized a series of honokiol/magnolol azo derivatives by introduction of the azo moiety into **1** and **2**. Their insecticidal activity was evaluated against the oriental armyworm (*Mythimna separata* Walker), an important and typical lepidopteran pest.

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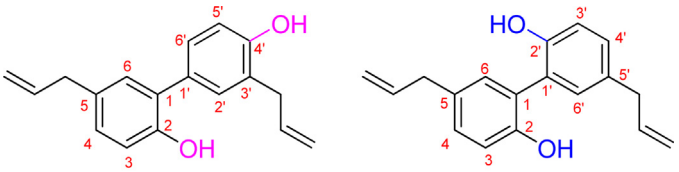


1 2

**Fig. 1.** Chemical structures of honokiol (**1**) and magnolol (**2**).

## 2. Materials and methods

### 2.1. General

All chemical reagents were purchased and utilized without further purification. Solvents were used directly or treated with standard methods before use. Melting points (mp) were determined on a XT-4 digital melting point apparatus (Beijing Tech Instrument Co., Ltd., Beijing, China) and were uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance 400 or 500 MHz instrument in $CDCl_3$ ($^1H$ at 400 or 500 MHz, and $^{13}C$ at 125 MHz) using tetramethylsilane (TMS) as the internal standard.

### 2.2. General procedure for the synthesis of honokiol/magnolol azo derivatives (*5a–q*, *6a–d, h–k*, and *7a–d, i, k*)

To a solution of arylamines **3a–q** (2.5 mmol) and concentrated HCl (12 mol/L, 0.62 mL) in water (5 mL) at 0 °C, a solution of sodium nitrite ($NaNO_2$, 2.7 mmol) in water (10 mL) was added dropwise. After adding, the mixture was further stirred for 30 min, and a solution of diazonium chlorides **4a–q** was prepared. Subsequently, a solution of **4a–q** was added gradually to a mixture of **1** (1 mmol) or a solution of **4a–d**, **h–k** was added gradually to a mixture of **2** (1 mmol), sodium hydroxide (NaOH, 2.2 mmol), and water (20 mL) at 0–5 °C. The pH value of the mixture was adjusted to 8–9 by use of 1.0 M aq. NaOH. After addition of the above diazonium solution, the pH value of the corresponding mixture was adjusted to 4–5 by use of 1.0 M aq. HCl. Then the mixture was continued to stir for 5–8 h until a lot of solid was precipitated. The solid was collected, washed with water (3 × 10 mL), dried and purified by preparative thin-layer chromatography (PTLC) to give the target products **5a–q**, **6a–d**, **h–k**, and **7a–d**, **i**, **k**.

*Data for* **5a**: Yield: 36%, red solid, m.p. 82–84 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.55 (s, 1H, -OH), 13.43 (s, 1H, -OH), 8.13 (s, 1H), 7.87–7.90 (m, 4H), 7.79 (s, 1H), 7.56 (s, 1H), 7.48–7.52 (m, 6H), 7.35 (s, 1H), 6.03-6.14 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.11-5.20 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.55 (d, $J$ = 5.5 Hz, 2H, -C<u>H</u>$_2$CH), 3.49 (d, $J$ = 5.5 Hz, 2H, -C<u>H</u>$_2$CH); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 150.46, 150.37, 150.31, 148.77, 137.31, 137.18, 136.80, 136.31, 134.86, 134.47, 132.15, 131.94, 131.40, 131.19, 131.07, 129.71, 129.41, 129.36, 128.90, 128.60, 122.25, 122.22, 116.28, 115.99, 39.20, 33.60.

*Data for* **5b**: Yield: 46%, red solid, m.p. 54–56 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.61 (s, 1H, -OH), 13.50 (s, 1H, -OH), 8.11 (s, 1H), 7.77–7.80 (m, 5H), 7.54 (s, 1H), 7.31–7.32 (m, 5H), 6.02-6.12 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.10–5.20 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.54 (d, $J$ = 5.5 Hz, 2H, -C<u>H</u>$_2$CH), 3.48 (d, $J$ = 6.0 Hz, 2H, -C<u>H</u>$_2$CH), 2.44 (s, 6H, 2×-$CH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 150.22, 148.68, 148.45, 148.38, 141.91, 141.76, 137.25, 137.21, 136.69, 136.38, 134.48, 134.09, 131.92, 131.68, 131.26, 130.07, 130.02, 129.67, 128.74, 128.57, 122.19, 122.16, 116.21, 115.91, 39.22, 33.62, 21.54.

*Data for* **5c**: Yield: 23%, red solid, m.p. 148–150 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 14.10 (s, 1H, -OH), 14.09 (s, 1H, -OH), 8.12 (s, 1H), 7.90–7.91 (m, 2H), 7.77 (s, 1H), 7.55 (s, 1H), 7.44–7.47 (m, 2H), 7.31 (s, 1H), 7.05–7.10 (m, 4H), 6.04–6.14 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.09–5.20 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 4.03 (s, 3H, -$OCH_3$), 3.98 (s, 3H, -$OCH_3$), 3.57 (d, $J$ = 4.0 Hz, 2H, -C<u>H</u>$_2$CH), 3.48 (d, $J$ = 4.5 Hz, 2H, -C<u>H</u>$_2$CH); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 156.21, 156.13, 150.80, 149.20, 138.88, 137.98, 137.51, 137.31, 136.52, 134.47, 134.16, 132.71, 132.56, 131.90, 131.63, 130.92, 130.10, 129.05, 128.51, 120.87, 116.20, 116.16, 115.84, 112.24, 112.21, 56.01, 55.96, 39.23, 33.60.

*Data for* **5d**: Yield: 25%, red solid, m.p. 146–148 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.56 (s, 1H, -OH), 13.46 (s, 1H, -OH), 8.07 (s, 1H), 7.84–7.86 (m, 4H), 7.73 (s, 1H), 7.51 (s, 1H), 7.30 (s, 1H), 6.99–7.01 (m, 4H), 6.04–6.12 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.10–5.19 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 4.10–4.14 (m, 4H, 2×-OC<u>H</u>$_2$$CH_3$), 3.54 (d, $J$ = 4.5 Hz, 2H, -C<u>H</u>$_2$CH), 3.48 (d, $J$ = 4.5 Hz, 2H, -C<u>H</u>$_2$CH), 1.45–1.47 (m, 6H, 2×-$OCH_2$C<u>H</u>$_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 161.64, 161.54, 150.03, 148.50, 144.43, 144.35, 137.33, 137.15, 136.63, 136.46, 133.99, 133.58, 131.55, 131.25, 131.16, 129.64, 128.61, 128.57, 124.00, 116.13, 115.84, 115.03, 114.98, 63.90, 39.25, 33.65, 14.74.

*Data for* **5e**: Yield: 36%, red solid, m.p. 46–48 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.65 (s, 1H, -OH), 13.53 (s, 1H, -OH), 8.13 (s, 1H), 7.79 (s, 1H), 7.68–7.72 (m, 4H), 7.56 (s, 1H), 7.39–7.42 (m, 2H), 7.35 (s, 1H), 7.29–7.31 (m, 2H), 6.04-6.13 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.11-5.20 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.55 (s, 2H, -C<u>H</u>$_2$CH), 3.50 (s, 2H, -C<u>H</u>$_2$CH), 2.45 (s, 6H, 2×-$CH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 150.43, 150.35, 150.30, 148.75, 139.39, 139.33, 137.25, 137.20, 136.75, 136.32, 134.71, 134.33, 132.08, 132.04, 131.92, 131.88, 131.31, 129.66, 129.21, 129.15, 128.82, 128.54, 122.27, 119.94, 119.88, 116.26, 115.96, 39.21, 33.61, 21.40.

*Data for* **5f**: Yield: 26%, red solid, m.p. 104–106 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.66 (s, 1H, -OH), 13.59 (s, 1H, -OH), 8.17 (s, 1H), 7.82–7.86 (m, 3H), 7.56 (s, 1H), 7.31–7.35 (m, 7H), 6.05–6.13 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.10–5.21 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.56 (d, $J$ = 5.0 Hz, 2H, -C<u>H</u>$_2$CH), 3.50 (d, $J$ = 5.0 Hz, 2H, -C<u>H</u>$_2$CH), 2.67 (s, 3H, -$CH_3$), 2.63 (s, 3H, -$CH_3$).

*Data for* **5g**: Yield: 20%, red solid, m.p. 70–72 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.37 (s, 1H, -OH), 13.23 (s, 1H, -OH), 8.11 (s, 1H), 7.82–7.85 (m, 4H), 7.77 (s, 1H), 7.56 (s, 1H), 7.48–7.50 (m, 4H), 7.35 (s, 1H), 6.02–6.11 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.11–5.20 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.54 (d, $J$ = 5.0 Hz, 2H, -C<u>H</u>$_2$CH), 3.49 (d, $J$ = 5.5 Hz, 2H, -C<u>H</u>$_2$CH); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 150.25, 148.88, 148.79, 148.66, 137.26, 137.14, 137.06, 137.00, 136.73, 136.18, 135.13, 134.76, 132.17, 132.03, 131.59, 129.70, 129.65, 129.60, 128.98, 128.60, 123.42, 123.39, 116.38, 116.07, 39.16, 33.58.

*Data for* **5h**: Yield:18%, red solid, m.p. 128–130 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.50 (s, 1H, -OH), 13.46 (s, 1H, -OH), 8.17 (s, 1H), 7.96–7.97 (m, 2H), 7.82 (s, 1H), 7.57–7.59 (m, 3H), 7.37–7.41 (m, 5H), 6.03–6.15 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.10–5.21 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.57 (d, $J$ = 6.0 Hz, 2H, -C<u>H</u>$_2$CH), 3.50 (d, $J$ = 6.0 Hz, 2H, -C<u>H</u>$_2$CH); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 150.30, 148.69, 146.43, 137.88, 137.38, 137.08, 136.18, 135.50, 135.26, 134.18, 134.05, 132.64, 132.52, 131.93, 131.81, 131.46, 130.58, 130.53, 129.96, 129.39, 128.58, 127.59, 117.48, 117.37, 116.38, 116.12, 39.14, 33.52.

*Data for* **5i**: Yield: 13%, dark red solid, m.p. 138–140 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.34 (s, 1H, -OH), 13.17 (s, 1H, -OH), 8.39–8.41 (m, 4H), 8.15 (s, 1H), 8.02–8.03 (m, 4H), 7.84 (s, 1H), 7.63 (s, 1H), 7.43 (s, 1H), 6.04–6.11 (m, 2H, 5-C<u>H</u>=$CH_2$ and 3′-C<u>H</u>=$CH_2$), 5.13–5.22 (m, 4H, 5-CH=C<u>H</u>$_2$ and 3′-CH=C<u>H</u>$_2$), 3.56 (d, $J$ = 5.5 Hz, 2H, -C<u>H</u>$_2$CH), 3.51 (d, $J$ = 5.5 Hz, 2H, -C<u>H</u>$_2$CH); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 153.86, 153.73, 150.84, 149.23, 148.65, 148.60, 137.80, 137.28, 136.74, 136.56, 136.24, 135.84, 132.83, 132.77, 132.20, 129.64, 129.55, 128.71, 125.09, 125.05, 122.78, 122.75, 116.70, 116.36, 39.08, 33.51.

*Data for* **5j**: Yield: 27%, red solid, m.p. 50–52 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 13.30 (s, 1H, -OH), 13.15 (s, 1H, -OH), 8.17