Alkylfurans: Effects of Alkyl Side-Chain Length on Insecticidal Activity

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JOURNAL OF NATURAL PRODUCTS®

Reprinted from
Volume 62, Number 1, Pages 191–193

Alkylfurans: Effects of Alkyl Side-Chain Length on Insecticidal Activity

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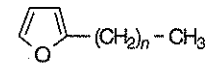
Received August 7, 1998

The insecticidal activity of five alkylfurans against the generalist insect herbivore beet armyworm, *Spodoptera exigua*, was examined. Two naturally occurring compounds, the avocadofurans 2-(pentadecyl)-furan (**1**) and 2-(heptadecyl)furan (**2**), previously isolated from specialized avocado idioblast oil cells, and three homologues, 2-(tetradecyl)furan (**3**), 2-(hexadecyl)furan (**4**), and 2-(octadecyl)furan (**5**), were synthesized. Bioassays of alkylfurans **1**−**5** using a 9-day diet-incorporation initiated with neonates showed that all alkylfurans tested significantly increased *S. exigua* larval mortality and reduced larval weights, with maximal biological activity detected among the naturally occurring alkylfurans **1** and **2**.

Compounds containing furan rings are found in many plant species.[1] However, except for a few specific phytochemicals such as furanocoumarins, few studies have examined their biological role. A group of these furan-containing compounds are present in avocados, *Persea americana* Mill (Lauraceae), and related plants. These compounds, commonly referred to as avocadofurans,[2,3] contain the furan moiety substituted at the second position with various saturated or unsaturated side chains. Avocadofurans were first identified by Kashman et al.,[4,5] who reported two avocadofurans, 2-(tridec-12-ynyl)furan and 2-(tridec-12-enyl)furan, from avocado fruit and seeds. Later, Magalhaes et al.[2] isolated and identified several new avocadofurans (avocadenofuran, avocadynofuran, avocadienofuran, and isoavocadienofuran) from avocado seed extracts. Since then, many other avocadofurans have been identified.[3,6−8]

Although avocadofurans were first isolated almost 30 years ago, little is known about their biological activity. Néeman et al.[6] were the first to report growth-inhibitory activity of an avocadofuran against the bacteria *Staphylococcus aureus* Rosenbach. Murakoshi et al.[7] tested the avocadofuran (8*Z*,11*Z*)-2-(8,11-heptadecadienyl)furan on silkworm larvae, *Bombyx mori* L; however, they reported no activity at concentrations in diet up to 300 μg g^{-1}. Recently, Rodriguez-Saona et al.[9] tested four avocadofurans and the triglyceride triolein, isolated from specialized idioblast oil cells of ripe avocado *P. americana* fruit,[10] against a generalist herbivore, *Spodoptera exigua* (Hübner). They reported 2-(pentadecyl)furan (**1**) and 2-(heptadecyl)-furan (**2**) as the most active compounds, with LC_{50}s of 1031 and 1206 μg g^{-1} in artificial diet, respectively.

This paper expands the Rodriguez-Saona et al.[9] project by studying the effects of alkyl side-chain length on larval mortality and growth of the generalist insect herbivore beet armyworm, *S. exigua*. A homologous series of 2-alkylfurans, with saturated side chains ranging from 14 to 18 carbons was synthesized and examined. Because the alkylfurans tested have similar structures, we hypothesized that avocados produce those that may confer the best protection against herbivores. Of the five alkylfurans studied, 2-(pentadecyl)furan (**1**) and 2-(heptadecyl)furan (**2**) are found in avocados.[9] The other three alkylfurans tested, 2-(tetradecyl)furan (**3**), 2-(hexadecyl)furan (**4**), and 2-(octadecyl)-furan (**5**), have never been reported to occur in either avocados or related plants.



1, $n = 14$
2, $n = 16$
3, $n = 13$
4, $n = 15$
5, $n = 17$

Results showed that all alkylfurans assayed significantly reduced 9-day larval weights ($p < 0.001$, $F = 50.31$, $df = 5, 184$) and increased larval mortality ($p < 0.001$, $F = 11.35$, $df = 5, 18$) compared to controls, at a concentration of 5 μmoles g^{-1} of diet. Of the alkylfurans tested, **3** had the lowest activity, with a mortality of less than 50% of *S. exigua* larvae, but significantly reduced larval weight (Figure 1) compared to untreated control. 2-(Octadecyl)-furan (**5**) was slightly less toxic (68% mortality) than **1**, **2**, and **4** (Figure 1). The two natural alkylfurans **1** and **2** showed the greatest mortality rates, 93% and 95%, respectively. These results indicate that, although all the furan compounds tested had detrimental effects to *S. exigua* early instars, the alkyl chain length affected their biological activity, with maximal mortality and greatest reduction of larval weights among **1**, **2**, and **4**.

Currently, the mode of action of the alkylfurans in insects is poorly understood, and it is unclear why there is such a difference between the 2-(tetradecyl)furan (**3**) and the other alkylfurans tested. Nonetheless, avocados produce the alkylfurans with the greatest detrimental effects against a generalist herbivore, suggesting that these compounds might play a role in plant defense against herbivory. Although applying avocadofurans, or related alkylfurans, to plants may provide a means of insect control, recent in vitro studies showed that furan-containing compounds from avocado seed oils can inhibit lysyl oxidase (protein-L-lysine: oxidoreductase), and might potentially serve as an antifibrotic drug in the treatment of diseases involving excess collagen and elastin deposition.[16] Thus, before the avocadofurans can be considered for commercialization as a new natural insecticide, additional information is necessary on field rates, mammalian toxicity, phytotoxicity, and persistence under field conditions.

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10.1021/np980340m CCC: $18.00
Published on Web 11/20/1998

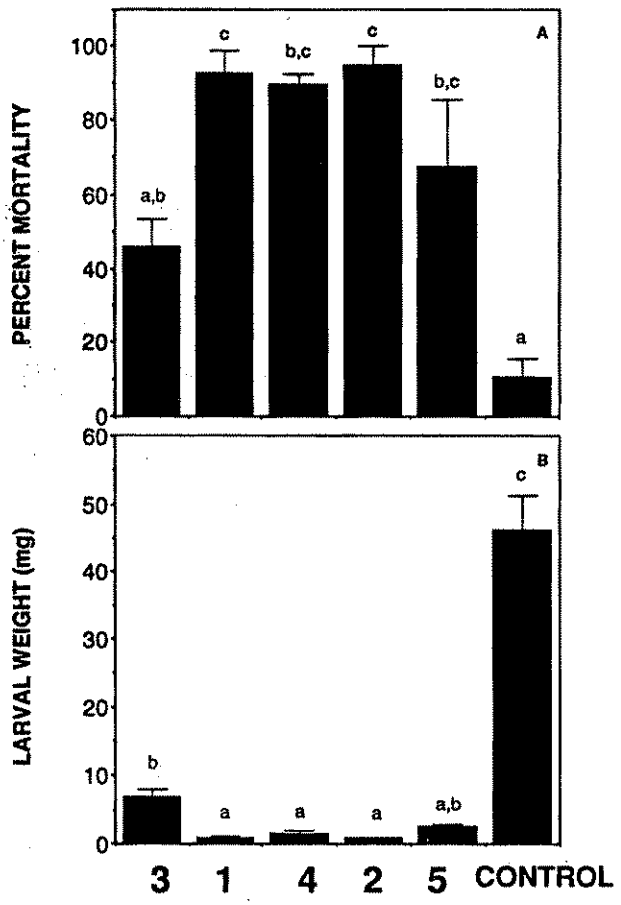

Figure 1. Percent mortality (**A**) and larval weights (**B**) of *Spodoptera exigua* larvae fed with different alkylfurans (**1**–**5**) incorporated into artificial diet at 5 μmoles g^{-1}. Bars represent standard errors. Treatment means with same letters are not significantly different at 5% level (Tukey Compromise Test). Larval weights refer only to the survivors after 9 days.

Experimental Section

General Experimental Procedures. The ^1H and ^{13}C NMR spectra were recorded at 270 and 67.9 MHz, respectively, in $CDCl_3$. The chemical shifts (δ) are reported in parts per million, and the coupling constants are reported in Hertz. IR spectra were obtained on a Mattson Galaxy Series 3000 FT-IR using KBr plates and CCl_4 as solvent. MS were obtained on a Shimadzu QP-5000 quadrapole GC/MS.

Insects. *S. exigua* larvae were used in all experiments. *S. exigua* is a polyphagous noctuid and a primary pest of agricultural crops in the United States and Mexico[11,12] that has developed resistance to many conventional insecticides.[13] However, it has not been reported to feed on avocados. Larvae were obtained from a colony originally collected from Orange Co., CA, in 1982, and maintained on artificial diet (modified from Patana[14]) at 28 ± 2 °C and 14:10 (L:D) photoperiod. New genetic material was incorporated into the colony within 12 months of the study. A standardized cohort of neonates within 12 h of eclosion was used in all bioassays. Incubator conditions were 28 ± 2 °C, 75% relative humidity, and 14:10 (L:D) photoperiod with fluorescent lighting for all experiments.

Alkylfurans. Two of the alkylfurans tested, 2-(pentadecyl)-furan (**1**) and 2-(heptadecyl)furan (**2**), were synthesized as described by Rodriguez-Saona et al.[9] The syntheses of the other three, previously unreported alkylfurans (**3**–**5**) bioassayed are as follows.

2-(Tetradecyl)furan (3). A mixture of dry THF (4 mL) and furan (1.05 mL, 0.98 g, 14.4 mmol) was cooled to −20 °C under N_2; *n*-BuLi (6.00 mL, 9.00 mmol, 1.5 M in hexane) was added dropwise, and the resulting solution was stirred 1 h, warmed to room temperature for 15 min, then recooled to −20 °C. 1-Bromotetradecane (2.05 g, 8.17 mmol) in THF (4 mL) was added dropwise, and the resulting solution was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The organic layer was removed, and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 5 mL) and brine (1 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was passed through a small Si gel plug and recrystallized in MeOH (ca. 50 mL/g, cooling to 5 °C) to afford the 2-(tetradecyl)furan: mp 8–10 °C (1.50 g, 77% yield); ^1H NMR δ 0.89 (3H, $-CH_3$, distorted triplet, $J \approx 6.6$ Hz), 1.26 (22 H, $-CH_2-$, br s), 1.63 (2H, H^2, quintet, $J \approx 7.2$ Hz), 2.60 (2H, H^1, t, $J \approx 7.4$ Hz), 5.96 (1H, Ar–H, dd, $J \approx 0.74$ Hz, 3.2 Hz), 6.26 (1H, Ar–H, dd, $J \approx 0.74$ Hz, 1.9 Hz), 7.27 (1H, Ar–H, dd, $J \approx 1.9$ Hz, 3.2 Hz); ^{13}C NMR δ 14.00, 22.79, 28.07, 28.14, 29.30, 29.47, 29.75, 29.76, 29.78, 29.80, 104.55, 110.07, 140.65, 156.70; IR υ 2860(s), 2790 (s), 1580 (m), 1440 (s), 1130 (m), 990 (m), 700 (s) cm^{-1}; MS 264 (7, M), 235 (2), 221 (2), 207 (3), 193 (3), 179 (4), 165 (4), 151 (3), 137 (4), 123 (4), 109 (21), 95 (91), 81 (base), 67 (25).

2-(Hexadecyl)furan (4). Following the procedure for the synthesis of 2-tetradecanylfuran, a solution of THF (4 mL) and furan (1.08 mL, 1.01 g, 14.8 mmol) was reacted with *n*-BuLi (5.3 mL, 7.90 mmol, 1.5 M in hexane), followed by 1-bromohexadecane (2.0 g, 6.58 mmol) in THF (4 mL). Workup and recrystallation afforded 2-hexadecylfuran: mp 18–20 °C (1.45 g, 76% yield); ^1H NMR δ 0.88 (3H, $-CH_3$, distorted triplet, $J \approx 6.7$ Hz) 1.26 (26 H, $-CH_2-$, br s), 1.63 (2H, H^2, quintet, $J \approx 7.2$ Hz), 2.60 (2H, H^1, t, $J \approx 7.4$ Hz), 5.96 (1H, Ar–H, dd, $J \approx 0.76$ Hz, 3.2 Hz), 6.26 (1H, Ar–H, dd, $J \approx 0.76$ Hz, 1.9 Hz), 7.27 (1H, Ar–H, dd, $J \approx 1.9$ Hz, 3.2 Hz); ^{13}C NMR δ 14.00, 22.79, 28.06, 28.13, 29.29, 29.46, 29.65, 29.73, 29.77 29.79, 104.55, 110.06, 140.65, 156.70; IR υ 2860(s), 2790 (s), 1580 (m), 1430 (s), 1125 (m), 980 (m), 700 (s) cm^{-1}; MS 292 (5, M), 263 (5), 249 (5), 235 (3), 221 (2), 207 (3), 193 (3), 179 (4), 165 (3) 151 (3), 137 (4), 123 (4), 109 (13), 95 (70), 81 (base), 67 (17).

2-(Octadecyl)furan (5). Following the procedure for the synthesis of 2-tetradecanylfuran, a solution of THF (4 mL) and furan (1.05 mL, 0.98 g, 14.4 mmol) was reacted with *n*-BuLi (7.2 mL, 10.8 mmol, 1.5 M in hexane), followed by 1-bromooctadecane (3.0 g, 9.01 mmol) in THF (4 mL). Workup and recrystallation afforded 2-(octadecyl)furan: mp 29–30 °C (2.61 g, 90% yield); ^1H NMR δ 0.85 (3H, $-CH_3$, distorted triplet, $J \approx 6.7$ Hz), 1.23 (28 H, $-CH_2-$, br s), 1.6 (2H, H^2, quintet, $J \approx 7.2$ Hz), 2.60 (2H, H^1, t, $J \approx 7.4$ Hz), 5.95 (1H, Ar–H, dd, $J \approx 0.76$ Hz, 3.1 Hz), 6.26 (1H, Ar–H, dd, $J \approx 0.76$ Hz, 1.9 Hz), 7.27 (1H, Ar–H, dd, $J \approx 1.9$ Hz, 3.1 Hz); ^{13}C NMR δ 14.19, 22.77, 28.06, 28.11, 29.26, 29.44, 29.63, 29.77, 32.00, 104.55, 110.07, 140.65, 156.71; IR υ 2926 (s), 2856 (m), 1461 (w), 1147 (w), 1007 (w), 732 (w) cm^{-1}; MS 320 (5, M), 291 (4), 277(5), 263 (3), 249 (2), 235 (2), 221 (2), 207 (3), 193 (3), 179 (2), 165 (2), 151 (3), 137 (5), 123 (12), 109 (11), 95 (87), 81 (base), 67 (23).

Bioassays. 2-(Tetradecyl)furan, 2-(pentadecyl)furan, 2-(hexadecyl)furan, 2-(heptadecyl)furan, and 2-(octadecyl)furan (> 95% purity) were tested for activity against *S. exigua* in diet bioassays. Treated diets were prepared at a concentration known to be insecticidal to *S. exigua* early instars for previously tested avocadofurans (5 μmoles g^{-1} diet).[9] Bioassays were conducted as described by Rodriguez-Saona et al.[9] Each furan compound, in Me_2CO solution, was transferred into a 50-mL polypropylene centrifuge tube (Fisher, Pittsburgh, PA); after the Me_2CO evaporated, 2 mL of 0.1% Tween-80 solution (Fisher) was added, homogenized with an ultrasonic homogenizer (Cole-Parmer, Chicago, IL), and artificial diet added to produce a final weight of 15 g. The mixture was vortexed for 3 min. Control diet was prepared by mixing 2 mL of Tween solution with 13 g of artificial diet to produce a final weight of 15 g. Control and treated diets were poured into 16-well bioassay trays (C-D International Inc., Pitman, NJ). One neonate was added per well. Trays were placed in an incubator set for conditions described above. Twenty-four neonates were tested for each treatment. Each treatment was replicated four times (total of 96 larvae/treatment). Larval mortality and

weight were recorded after 9 days. Data were analyzed using ANOVA.[15] Mortality data was transformed using the arcsine square-root transformation, while a log transformation was used for the data on larval weights. Multiple comparisons were performed using the Tukey Compromise test ($\alpha = 0.05$). Control mortality for all bioassays was $\leq 10\%$.

Acknowledgment. We thank the laboratory assistance of K. White, J. Young, G. Kund, and W. Carson. We are grateful to Drs. K. Platt and W. Thomson (Department of Botany, University of California, Riverside) and Dr. J. Millar (Department of Entomology, University of California, Riverside) for their advice and support. This project was supported in part by the California Celery Research Advisory Board and the California Tomato Commission.

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NP980340M