Bioscience, Biotechnology, and Biochemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tbbb20

Syntheses and Biological Activities of Pyranyl-substituted Cinnamates

Jun ZHU[a], Motoji MAJIKINA[a] & Shinkichi TAWATA[a]
[a] Faculty of Agriculture, University of the Ryukyus
Published online: 22 May 2014.

To cite this article: Jun ZHU, Motoji MAJIKINA & Shinkichi TAWATA (2001) Syntheses and Biological Activities of Pyranyl-substituted Cinnamates, Bioscience, Biotechnology, and Biochemistry, 65:1, 161-163, DOI: 10.1271/bbb.65.161

To link to this article: http://dx.doi.org/10.1271/bbb.65.161

Biosci. Biotechnol. Biochem., **65** (1), 161–163, 2001

Note

Syntheses and Biological Activities of Pyranyl-substituted Cinnamates

Jun ZHU, Motoji MAJIKINA, and Shinkichi TAWATA†

Faculty of Agriculture, University of the Ryukyus, Senbaru 1, Nishihara-cho, Nakagami-gun, Okinawa 903-0129, Japan

Received April 27, 2000; Accepted August 18, 2000

Twenty-two kinds of pyranyl-substituted cinnamates were synthesized by the reaction of 4-hydroxy-6-(2-phenylethyl)-2*H*-pyran-2-one or 4-hydroxy-6-methyl-2*H*-pyran-2-one (HMP) with a variety of substituted cinnamic acids, and their antifungal and plant growth inhibitory activities were investigated. Among the compounds prepared, 6-methyl-2-oxo-2*H*-pyran-4-yl 3-(4-isopropylphenyl)propenoate (H5) showed the strongest antifungal activity against *Rhizoctonia solani* and *Sclerotium dellfinii*, and 6-methyl-2-oxo-2*H*-pyran-4-yl 3-(2-methylphenyl)propenoate (H2) had the highest plant growth inhibitory activity toward *Brassica rapa*.

Key words: cinnamate; pyran; 7,8-dihydro-5,6-dehydrokawain; antifungal activity; plant growth inhibition

7,8-Dihydro-5,6-dehydrokawain (DDK), *i.e.*, 4-methoxy-6-(2-phenylethyl)-2*H*-pyran-2-one, which was isolated from the rhizomes of *Alpinia speciosa* K. Schum., has been found to have an antiulcer effect and antiplatelet action.[1,2] Fujita *et al.* have reported that the DDK derivatives substituted at the phenyl ring inhibited the hypocotyl growth in lettuce seedlings.[3] Organophosphorus esters derived from DDK have been reported to show insecticidal and antifungal activities.[4] On the other hand, cinnamic acid derivatives have been studied for their antioxidative and antibacterial activities.[5-8] In our previous paper, many of the cinnamates with the components of essential oil in *A. speciosa* showed antifungal activity against plant pathogenic fungi.[9,10] Since DDK derivatives with a cinnamoyl group have not previously been reported, we describe the synthesis of such derivatives and their biological activity, and explain the relationship between the activity and substituents on the aromatic ring of the cinnamoyl moiety.

The structures of twenty-two kinds of pyranyl-substituted cinnamates are shown in Fig. 1. Substituted cinnamic acids were prepared by using the Claisen condensation reaction from substituted benzaldehydes and malonic acid.[11-13] Compounds **D1–D11** were prepared from the reaction of these substituted cinnamic acids and 4-hydroxy-6-(2-phenylethyl)-2*H*-pyran-2-one, which had been obtained by the hydrolysis of DDK with conc. HCl.[4] Compounds **H1–H11** were prepared by using 4-hydroxy-6-methyl-2*H*-pyran-2-one (HMP), which has the partial skeleton of DDK. The subsequent procedure for the synthesis of compound **D5** is typical. To a dichloromethane solution (20 ml) of 4-isopropylcinnamoyl chloride, which had been obtained from the reaction of thionyl chloride (20 ml) and 4-isopropyl cinnamic acid (2 mmol, 0.38 g), triethylamine (2 mmol, 0.20 g) and 4-hydroxy-6-(2-phenylethyl)-2*H*-pyran-2-one (1.4 mmol, 0.3 g) were added. After stirring for 6 h at room temperature, the solution was evaporated *in vacuo*. The resulting residue was purified by preparative TLC (Kieselgel 60 PF_{254}, 20 × 20 cm, 2.0 mm layer thickness, Merck) to yield 0.18 g (25.0%) of 6-(2-phenylethyl)-2-oxo-2*H*-pyran-4-yl 3-(4-isopropylphenyl)propenoate (**D5**) as an oil.[14]

The antifungal activities of the pyranyl-substituted

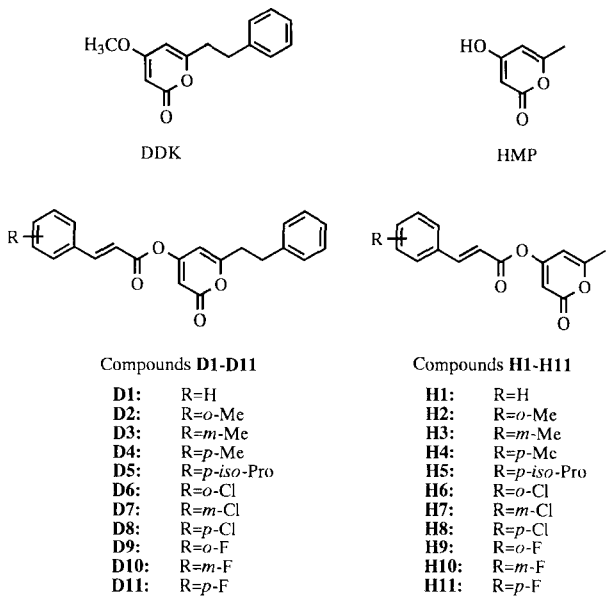

Fig. 1. Structures of DDK, HMP and the Pyranyl-substituted Cinnamates.

† To whom correspondence should be addressed. Tel: +81-98-895-8803; Fax: +81-98-895-2864; E-mail: b986097@agr.u-ryukyu.ac.jp

Abbreviations: DDK, 7,8-dihydro-5,6-dehydrokawain; HMP, 4-hydroxy-6-methyl-2*H*-pyran-2-one

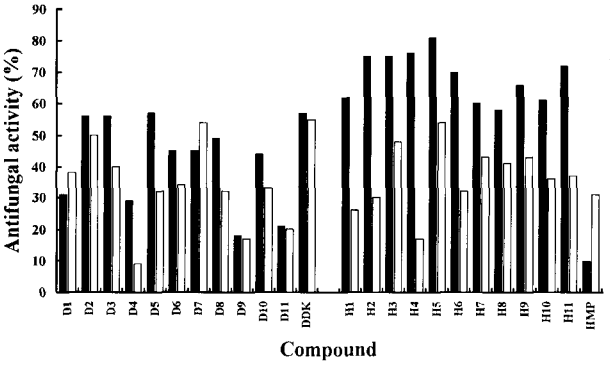

Fig. 2. Antifungal Activity of the Pyranyl-substituted Cinnamates.

Refer to Fig. 1 for the structural data. The fungus was cultured in potato dextrose agar (PDA, 1.5% agar) for four days at 27°C and then used for testing. The antifungal activity was measured according to Taira *et al.*[15] and is expressed as the percentage inhibition. The assays were performed in triplicate, the test concentration being 100 ppm. The antifungal activity is shown as the growth inhibition (%) against a fungus compared to that of the control. ■ *R. solani*, □ *S. dellfinii*.

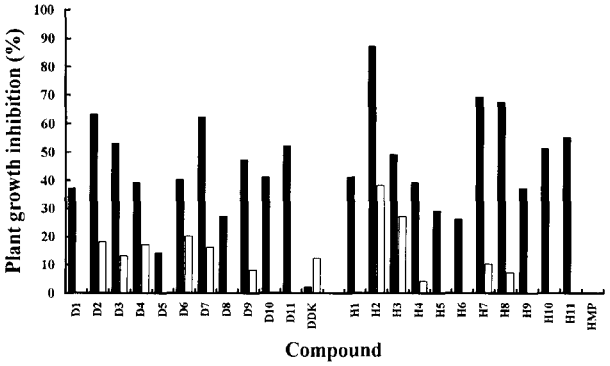

Fig. 3. Plant Growth Inhibitory Activity of the Pyranyl-substituted Cinnamates.

Refer to Fig. 1 for the structural data. *Brassica rapa* seeds were used to test the plant growth inhibition. Ten grains of seed were sown on filter paper in a Petri dish containing a test compound and 5 ml of a 0.3% aqueous solution of agricultural spreader (Approach BI). They were kept for three days at 27°C in the dark, and the lengths of the radicle and hypocotyl were measured. The plant growth inhibitory activity (%) is expressed in comparison with that of the control. Each experiment was conducted three times. ■ radicle, □ hypocotyl.

cinnamates against *R. solani* and *S. dellfinii* are shown in Fig. 2. DDK had relatively high antifungal activity against both fungi, but cinnamoyl derivative **D1** showed lower activity than that of DDK. Compounds **D2**, **D3** and **D5**, having a methyl or an isopropyl group on the aromatic ring of the cinnamoyl moiety, had higher activity than **D1** against *R. solani*. By introducing a chlorine atom into the aromatic ring (**D6–D8**), the antifungal activity against *R. solani* was slightly increased compared with that of the unsubstituted derivative (**D1**). When a fluorine atom was introduced, the resulting compounds (**D9–D11**) showed weak activity. The antifungal activity of the HMP derivatives was significantly stronger than that of HMP against *R. solani*. Compound **H5**, with an isopropyl group at the 4-position of the aromatic ring, showed the highest antifungal activity against both fungi among the prepared derivatives. The introduction of a chlorine or a fluorine atom into the cinnamoyl moiety (**H6–H11**) slightly enhanced the activity against *S. dellfinii* compared with that of the unsubstituted derivative (**H1**); however, their activity against *R. solani* was almost the same. Comparing the derivatives with the same substituents in the cinnamoyl moiety, it seems that the HMP derivatives showed higher antifungal activity than the DDK derivatives against *R. solani*.

The plant growth inhibitory activity of the compounds toward *B. rapa* is shown in Fig. 3. DDK did not have any significant effect on radicle or hypocotyl growth, while most of the cinnamate derivatives inhibited the growth of the radicle. When treated with **D2** and **D7**, the radicle growth was inhibited by more than 60% compared with that of the control. HMP had no inhibitory effect on the growth of either the radicle or hypocotyl at 100 ppm; however, the HMP derivatives with a substituted cinnamoyl group showed some growth inhibitory activity. Among the compounds prepared, 6-methyl-2-oxo-2*H*-pyran-4-yl 3-(2-methylphenyl)propenoate (**H2**) showed the highest plant growth inhibitory activity in the *B. rapa* seedling test.

It is noteworthy that the 4-isopropyl derivatives (**D5** and **H5**) showed relatively high antifungal activity against *R. solani* and *S. dellfinii*, but did not cause any significant injury to *B. rapa* seedlings.

Acknowledgments

We are grateful to Dr. Seiichi Yogi of the Faculty of Science, University of the Ryukyus for mass measurements. We also thank Dr. Zenichi Moromizato of the Faculty of Agriculture, University of the Ryukyus for providing the fungi and for his helpful advice.

References

1) Lin, J.-H., Studies on the antiulcer components of the rhizome of *Alpinia speciosa* K. Schumann. *Kou Li Chung-kuo I Yao Yen Chiu So Yen Chiu Pao Kao* (in Chinese), 147–162 (July 1982).
2) Teng, C.-M., Hsu, S.-Y., Lin, C.-H., Yu, S.-M., Wang, K.-J., Lin, M.-H., and Chen, C.-F., Antiplatelet action of dehydrokawain derivatives isolated from *Alpinia speciosa* rhizomes. *Chin. J. Physiol.*, **33**, 41–48 (1990).
3) Fujita, T., Nishimura, H., Kaburaki, K., and Mizutani, J., Plant growth inhibiting α-pyrones from *Alpinia speciosa*. *Phytochemistry*, **36**, 23–27 (1994).
4) Tawata, S., Taira, S., Kobamoto, N., Ishihara, M.,

and Toyama, S., Syntheses and biological activities of dihydro-5,6-dehydrokawain derivatives. *Biosci. Biotechnol. Biochem.*, **60**, 1643–1645 (1996).
5) Foti, M., Piattelli, M., Baratta, M. T., and Ruberto, G., Flavonoids, coumarins, and cinnamic acids as antioxidants in a micellar system. Structure-activity relationship. *J. Agric. Food Chem.*, **44**, 497–501 (1996).
6) Natella, F., Nardini, M., Felice, M. D., and Scaccini, C., Benzoic and cinnamic acid derivatives as antioxidants: Structure-activity relation. *J. Agric. Food Chem.*, **47**, 1453–1459 (1999).
7) Ray, S. K., Kumar, S., Sibal, M., and Rudra, S., Residual information flow, a newly developed electronic parameter, in the QSAR study of antifungal cinnamic acid derivatives. *Med. Sci. Res.*, **18**, 341–343 (1990).
8) Ray, S. K., Premakanth, K. L., Sekar, R. C., Murthy, M. V. S., Sridhar, V., Marasimhan, S. L., and Rudra, S., Design of potent antifungal cinnamic acid derivatives: a comparative multiparametric QSAR study involving newly developed electronic parameters, residual information flow and residual electronic force. *Med. Sci. Res.*, **19**, 759–763 (1991).
9) Tawata, S., Taira, S., Kobamoto, N., Zhu, J., Ishihara, M., and Toyama, S., Synthesis and antifungal activity of cinnamic acid esters. *Biosci. Biotechnol. Biochem.*, **60**, 909–910 (1996).
10) Zhu, J., Zhu, H., Kobamoto, N., Yasuda, M., and Tawata, S., Fungitoxic and phytotoxic activities of cinnamic acid esters and amides. *J. Pesticide Sci.*, **25**, 263–266 (2000).
11) Ragoussis, N., Modified Knoevenagel condensations. Synthesis of (*E*)-3-alkenoic acids. *Tetrahedron Lett.*, **28**, 93–96 (1987).
12) Richard, A. H., Use of dimethylformamide as a solvent for the Knoevenagel reaction. *J. Chem. Soc. Perkin I*, 1379–1380 (1974).
13) Tanikaga, R., Konya, N., Hamamura, K., and Kaji, A., Stereochemical behavior of intermediary compounds in the amine-catalyzed Knoevenagel reaction. *Bull. Chem. Soc. Jpn.*, **61**, 3211–3216 (1988).
14) Compound D5: n_D: 1.6120 (25.2°C); IR ν_{max} (KBr) cm^{-1}: 1741 (C=O), 1735 (C=O). NMR δ_H (270 MHz, $CDCl_3$): 1.25 (6H, d, J=7.3 Hz), 2.77 (2H, t, J=7.6 Hz), 2.89 (1H, sep, J=7.3 Hz), 2.97 (2H, t, J=7.6 Hz), 6.01 (1H, s), 6.18 (1H, s), 6.45 (1H, d, J=15.9 Hz), 7.15–7.50 (9H, m, aromatic), 7.82 (1H, d, J=15.9 Hz). NMR δ_C (68 MHz, $CDCl_3$): 23.4, 32.6, 33.9, 35.4, 100.8, 101.0, 101.1, 114.1, 126.2, 127.0, 128.0, 128.4, 128.5, 130.9, 139.4, 148.6, 152.7, 162.7, 163.0, 163.6, 165.2. EIMS (70 eV) m/z: 388 (M^+, 25), 360 (72), 216 (87), 190 (6), 173 (100), 131 (38), 105 (6), 91 (36), 69 (5), 43 (10). *Anal.* Found: C, 76.53; H, 6.31%. Calcd. for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23%.
15) Taira, S., Tawata, S., Kobamoto, N., Toyama, S., and Yasuda, M., Synthesis and fungicidal activity of new 1,3,2-oxazaphospholidine 2-sulfides. *J. Pesticide Sci.*, **19**, 299–304 (1994).