

# Crotonkinins A and B and related diterpenoids from *Croton tonkinensis* as anti-inflammatory and antitumor agents

Kuo P.-C., Shen Y.-C., Yang M.-L., Wang S.-H., Tran D.T., Nguyen X.D., Chiang P.-C., Lee K.-H., Lee E.-J., Wu T.-S.

Department of Biotechnology, National Formosa University, Yunlin 632, Taiwan; National Research Institute of Chinese Medicine, Taipei 112, Taiwan; Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan; Department of Chemistry, Vinh University, Vinh City, Viet Nam; Department of Chemistry, College of Natural Sciences, Hanoi National University, Hanoi 10000, Viet Nam; Natural Products Research Laboratories, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, United States; Departments of Surgery and Anesthesiology, Institute of Biomedical Engineering, National Cheng Kung University, Tainan, Taiwan; Department of Applied Chemistry, Providence University, Taichung 433, Taiwan

**Abstract:** Cytotoxicity-guided phytochemical investigation of a methanolic extract of *Croton tonkinensis* afforded two new kaurane diterpenoids (1, 2) and 10 known ent-kaurane-type diterpenoids (3-12). The structures of 1 and 2 were based on analysis of spectroscopic and mass spectral data. Compounds 3-12 were identified by comparison of their spectroscopic and physical data with those reported in the literature. Selected compounds from this plant were examined for cytotoxic and anti-inflammatory activities. Compounds 4 and 9 showed the highest cytotoxic activity against the tested tumor cell lines. Compounds 3, 4, 6, 8, 9, and 11 had  $IC_{50}$  values less than 5  $\mu$ M and were more potent than the nonspecific NOS inhibitor L-NAME in inhibiting LPS-induced NO production. © 2007 American Chemical Society and American Society of Pharmacognosy.

**Index Keywords:** *Croton tonkinensis* extract; crotonkinin a; crotonkinin b; diterpenoid; ent 18 acetoxy 7 $\alpha$ ,14 $\beta$  dihydroxykaur 16 en 15 one; ent 18 acetoxy 7 $\beta$  hydroxykaur 15 one; ent 18 acetoxykaur 16 en 15 one; ent 18 hydroxykaur 16 en 15 one; ent 1 $\beta$  acetoxy 7  $\alpha$ ,14 $\beta$  dihydroxykaur 16 en 15 one; ent 7  $\alpha$ ,14 $\beta$  dihydroxykaur 16 en 15 one; ent 7 $\beta$  hydroxy 15 oxokaur 16 en 18 ol; ent 7 $\beta$  hydroxy 15 oxokaur 16 en 18 yl acetate; ent 7 $\beta$  hydroxy 16 kauren 15 one; ent kaur 16 en 15 one 18 oic acid; kaurane derivative; lipopolysaccharide; methanol; n(g) nitroarginine methyl ester; nitric oxide; plant extract; unclassified drug; animal cell; antiinflammatory activity; antineoplastic activity; article; controlled study; *Croton tonkinensis*; cytotoxicity; drug isolation; drug structure; Euphorbia; human; human cell; mass spectrometry; medicinal plant; nonhuman; nuclear magnetic resonance spectroscopy; tumor cell; Anti-Inflammatory Agents, Non-Steroidal; Antineoplastic Agents, Phytogetic; Croton; Diterpenes; Drug Screening Assays, Antitumor; Humans; Inhibitory Concentration 50; Lipopolysaccharides; Molecular Structure; NG-Nitroarginine Methyl Ester; Nitric Oxide; Plants, Medicinal; Vietnam; *Croton tonkinensis*

Year: 2007

Source title: Journal of Natural Products

Volume: 70

Issue: 12

Page : 1906-1909

Cited by: 4

Link: Scopus Link

Chemicals/CAS: methanol, 67-56-1; n(g) nitroarginine methyl ester, 50903-99-6; nitric oxide, 10102-43-9; Anti-Inflammatory Agents, Non-Steroidal; Antineoplastic Agents, Phytogetic; Diterpenes; Lipopolysaccharides; NG-Nitroarginine Methyl Ester, 50903-99-6; Nitric Oxide, 10102-43-9; crotonkinin A; crotonkinin B

Correspondence Address: Wu, T.-S.; Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan; email: tswu@mail.ncku.edu.tw

ISSN: 1633864

CODEN: JNPRD

DOI: 10.1021/np070383f

PubMed ID: 18161942

Language of Original Document: English

Abbreviated Source Title: Journal of Natural Products

Document Type: Article

Source: Scopus

Authors with affiliations:

1. Kuo, P.-C., Department of Biotechnology, National Formosa University, Yunlin 632, Taiwan
2. Shen, Y.-C., National Research Institute of Chinese Medicine, Taipei 112, Taiwan
3. Yang, M.-L., Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan
4. Wang, S.-H., Department of Biotechnology, National Formosa University, Yunlin 632, Taiwan
5. Tran, D.T., Department of Chemistry, Vinh University, Vinh City, Viet Nam
6. Nguyen, X.D., Department of Chemistry, College of Natural Sciences, Hanoi National University, Hanoi 10000, Viet Nam
7. Chiang, P.-C., Natural Products Research Laboratories, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, United States
8. Lee, K.-H., Natural Products Research Laboratories, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, United States
9. Lee, E.-J., Departments of Surgery and Anesthesiology, Institute of Biomedical Engineering, National Cheng Kung University, Tainan, Taiwan
10. Wu, T.-S., Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan, Department of Applied Chemistry, Providence University, Taichung 433, Taiwan

References:

1. Hsieh, C.F., (1993) Flora of Taiwan, 3, p. 454. , Epoch: Taiwan
2. Vo, V.C., (1997) Dictionary of Vietnamese Medicinal Plants
3. Publishing House Medicine: Ho Chi Minh City, pp. 622-623
4. (1999) Selected Medicinal Plants in Vietnam, 1, pp. 260-262. , Publishing House Science and Technology: Hanoi
5. Do, T.L., (2001) Medicinal Plants and Remedies of Vietnam, p. 826. , Publishing House Medicine: Hanoi
6. Son, P.T., Giang, P.M., Taylor, W.C., (2000) Aust. J. Chem, 53, pp. 1005-1003
7. Minh, P.T.H., Ngoc, P.H., Quang, D.N., Hashimoto, T., Takaoka, S., Asakawa, Y., (2003) Chem. Pham. Bull, 51, pp. 590-

8. Giang, P.M., Jin, H.Z., Son, P.T., Lee, J.H., Hong, Y.S., Lee, J.J., (2003) *J. Nat. Prod*, 66, p. 1220
9. Minh, P.T.H., Ngoc, P.H., Taylor, W.C., Cuong, N.M., (2004) *Fitoterapia*, 75, pp. 556-552
10. Giang, P.M., Son, P.T., Lee, J.H., Otsuka, H., (2004) *Chem. Pharm. Bull*, 52, pp. 882-879
11. Giang, P.M., Son, P.T., Hamada, Y., Otsuka, H., (2005) *Chem. Pharm. Bull*, 53, pp. 296-300
12. Lorimer, S.D., Weavers, R.T., (1987) *Phytochemistry*, 26, pp. 3215-3207
13. Buchanan, M.S., Connolly, J.D., Kadir, A.A., Rycroft, D.S., (1996) *Phytochemistry*, 42, pp. 1641-1646
14. Asakawa, Y., Takikawa, K., Toyota, M., Ueda, A., Tori, M., Kumar, S.S., (1987) *Phytochemistry*, 26, pp. 1019-1022
15. Fraga, B.M., Gonzalez, P., Guillermo, R., Hernandez, M.G., (1996) *Tetrahedron*, 52, pp. 13767-13782
16. Perry, N.B., Burgess, E.J., Baek, S.H., Weavers, R.T., Geis, W., Mauger, A.B., (1999) *Phytochemistry*, 50, pp. 423-433
17. Weiss Jr., A.C., Elliger, C.A., Haddon, W.F., Benson, M., (1993) *J. Nat. Prod*, 56, pp. 1365-1372
18. Lee, K.H., Huang, E.S., Piantadosi, C., Pagano, J.S., Geissman, T.A., (1971) *Cancer Res*, 31, pp. 1649-1654
19. Lee, K.H., Hall, I.S., Mar, E.C., Starnes, C.O., ElGebaly, S.A., Waddell, T.G., Hadgraft, R.I., Weidner, I., (1977) *Science*, 196, pp. 533-535
20. Dringen, R., (2005) *Antioxid. Redox Signaling*, 7, pp. 1233-1223
21. Li, J., Baud, O., Vartanian, T., Volpe, J.J., Rosenberg, P.A., (2005) *Proc. Natl. Acad. Sci. U.S.A*, 102, pp. 9936-9941
22. Pacher, P., Beckman, J.S., Liaudet, L., (2007) *Physiol. Rev*, 87, pp. 315-424
23. Wang, Y.H., Wang, W.Y., Chang, C.C., Liou, K.T., Sung, Y.J., Liao, J.F., Chen, C.F., Shen, Y.C., (2006) *J. Biomed. Sci*, 13, pp. 127-141
24. Di Rosa, M., Radomski, M., Carnuccio, R., Moncada, S., (1990) *Biochem. Biophys. Res. Commun*, 172, pp. 1246-1252
25. Van den Worm, E., Beukelman, C.J., Van den Berg, A.J., Kroes, B.H., Labadie, R.P., Van Dijk, H., (2001) *Eur. J. Pharmacol*, 433, pp. 225-230
26. Lin, L.C., Wang, Y.H., Hou, Y.C., Chang, S., Liou, K.T., Chou, Y.C., Wang, W.Y., Shen, Y.C., (2006) *J. Pharm. Pharmacol*, 58, pp. 129-135
27. Liou, K.T., Shen, Y.C., Chen, C.F., Tsao, C.M., Tsai, S.K., (2003) *Eur. J. Pharmacol*, 475, pp. 19-27
28. Cheng, M.J., Lee, S.J., Chang, Y.Y., Wu, S.H., Tsai, I.L., Jayaprakasam, B., Chen, I.S., (2003) *Phytochemistry*, 63, pp. 603-608
29. Wang, X., Bastow, K.F., Sun, C.M., Lin, Y.L., Yu, H.J., Don, M.J., Wu, T.S., Lee, K.H., (2004) *J. Med. Chem*, 47, pp. 5816-5819