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Authors

Wenhui Pan, Kanglun Liu, Yifu Guan, Ghee Teng Tan, Nguyen Van Hung, Nguyen Manh Cuong, D. Doel Soejarto, John M. Pezzuto, Harry H. S. Fong, and Hongjie Zhang

Bioactive Compounds from *Vitex leptobotrys*[#]

Wenhui Pan,[†] Kanglun Liu,[†] Yifu Guan,[†] Ghee Teng Tan,[‡] Nguyen Van Hung,[§] Nguyen Manh Cuong,[⊥] D. Doel Soejarto,^{||} John M. Pezzuto,[‡] Harry H.S. Fong,^{||} and Hongjie Zhang^{*†}

[†]School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong SAR, People's Republic of China

[‡]College of Pharmacy, University of Hawaii at Hilo, Hilo, HI 96720, United States

[§]Institute of Marine Biochemistry of the Vietnam Academy of Science and Technology (VAST), Cau Giay, Hanoi

[⊥]Cuc Phuong National Park, Nho Quan, Ninh Binh, Vietnam

^{||}Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612, United States

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ABSTRACT: A new lignan, vitexkarinol (**1**), as well as a known lignan, neopaulownin (**2**), a known chalcone, 3-(4-hydroxyphenyl)-1-(2,4,6-trimethoxyphenyl)-2-propen-1-one (**3**), two known dehydroflavones, tsugafolin (**4**) and alpinetin (**5**), two known dipeptides, aurantiamide and aurantiamide acetate, a known sesquiterpene, vemopolyanthofuran, and five known carotenoid metabolites, vomifoliol, dihydrovomifoliol, dehydrovomifoliol, loliolide and isolololide, were isolated from the leaves and twigs of *Vitex leptobotrys* through bioassay-guided fractionation. The chalcone (**3**) was found to inhibit HIV-1 replication by 77% at 15.9 μM , and the two dehydroflavones (**4** and **5**) showed weak anti-HIV activity with IC_{50} values of 118 and 130 μM , respectively, while being devoid of cytotoxicity at 150 μM . A chlorophyll-enriched fraction of *V. leptobotrys*, containing pheophorbide *a*, was found to inhibit the replication of HIV-1 by 80% at a concentration of 10 $\mu\text{g/mL}$. Compounds **1** and **3** were further selected to be evaluated against 21 viral targets available at NIAID (National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD).

Acquired immunodeficiency syndrome (AIDS) has become a worldwide pandemic since its first report in 1981 in the United States.¹ It is a virally transmitted infectious disease with an especially high prevalence rate in sub-Saharan Africa and South Asia.^{2,3} More than 34 million people are living with HIV globally.² Despite much progress in anti-HIV therapy over the past two decades, the quest for safe and efficacious antiretroviral drugs remains elusive since current chemotherapeutic strategies are associated with significant adverse effects and the emergence of multidrug resistance. Natural product alternatives to synthetic drugs remain a desirable option even if such approaches are not yet viable. The urgency to replenish the anti-HIV armamentarium has provided impetus for the continued discovery of natural product lead molecules that possess potent antiretroviral activity to bolster the current pipeline of agents under development.⁴ Natural products are regarded as vital sources for drug discovery in terms of their diversified chemical structures as well as their functional roles in living organisms.^{5,6} Studies have shown that natural products may play important roles in defending plants from foreign invaders such as viruses. The roles that natural products play in the self-defense mechanisms of the plant host make them particularly attractive for the discovery of novel antiviral compounds from plants.⁷ Various natural products from higher plants have been reported to exhibit anti-HIV activity in the last two decades.⁸⁻¹²

As part of an ICBG (International Cooperative Biodiversity Groups) project that aims to identify anti-HIV agents from the plants of Vietnam and Laos,¹³ *Vitex leptobotrys* H. Hallier (Lamiaceae) was selected for further bioassay-directed fractionation based on positive results in preliminary screening. Although steroids, chalcones and an amine were

isolated from this plant species,¹⁴⁻¹⁶ no prior antiviral pharmacological report on this plant was recorded. However, several species in the genus *Vitex* have been used therapeutically in countries in Asia, being reported to have analgesic, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, antihistamine, and antiasthmatic activities.¹⁷ The genus *Vitex* contains about 250 species distributed around the world.¹⁸ Plants in this genus produce a variety of potentially bioactive molecules, such as flavonoids, terpenoids, steroids, iridoids and lignans.¹⁹ Our previous studies have led to the isolation of a series of novel diterpene amides from the chaste tree (*Vitex agnus-castus*).^{20,21} In a search for antiviral compounds from plants, it was determined that the chloroform extract of the leaves and twigs of *V. leptobotrys* inhibited HIV by 66% at 20 µg/mL without showing any toxicity to the host cells at the same concentration. A relatively large quantity of the plant material (3.6 kg) was then re-collected from the same tree to carry out bioassay-guided fractionation in order to isolate the anti-HIV active compounds. Accordingly, 13 compounds were isolated and identified including one new lignan (**1**), under bioassay-guided phytochemical separation. The current paper describes the isolation, identification, structure elucidation, and biological evaluation of these isolates from this species.

interpretation. In the HMBC spectrum of **1** (Figure 1), the H-7 (δ_{H} 4.54) signal showed correlations with C-1 (δ_{C} 128.4), C-2 (δ_{C} 107.4), C-6 (δ_{C} 120.1), C-8 (δ_{C} 85.8), C-9 (δ_{C} 75.06), C-8' (δ_{C} 88.3) and C-9' (δ_{C} 75.12); and the H-7' (δ_{H} 4.52) resonance was correlated with C-1' (δ_{C} 130.5), C-2' (δ_{C} 105.7), C-6' (δ_{C} 118.1), C-8' (δ_{C} 88.3), C-9' (δ_{C} 75.12), C-8 (δ_{C} 85.8), and C-9 (δ_{C} 75.06). From the ^1H NMR spectrum, two broad singlets at δ_{H} 2.51 and δ_{H} 3.62 were observed for two hydroxy groups, which were assigned to C-8 and C-8'. On the basis of these data and biogenetic considerations, compound **1** was determined as a furofuran lignan.

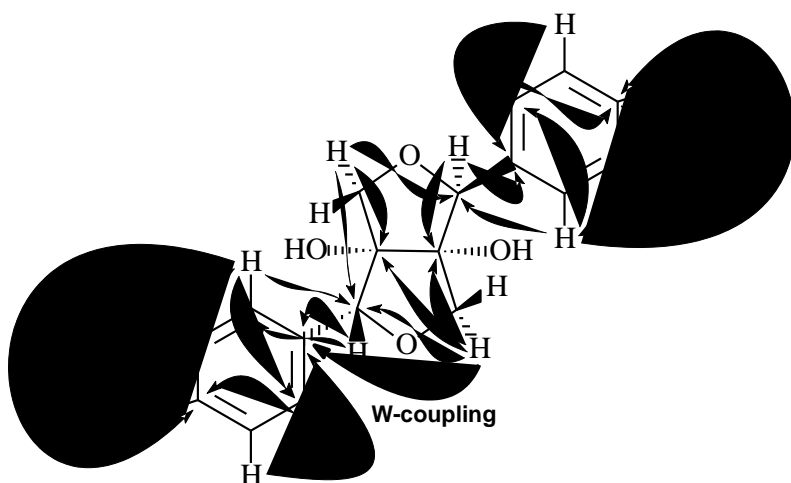
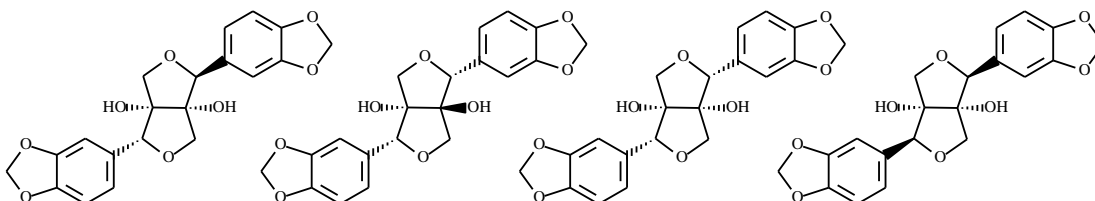


Figure 1. Selected HMBC correlations for compound **1** (CDCl_3).

Four possible structures with relative configurations can be presumed for **1** (Figure 2). The four structures differ from one another only by the stereochemistry at the four chiral centers.



of **F** rather than **E** (Figure 4). In the former case, the ROEs would be observed of H-7 to both H-9 β and H-9' β as well as the ROEs of H-7' to the two H-9 protons in the ROESY spectrum. Instead, only the ROE correlations of H-7 (δ_{H} 4.54) to H-9 β (δ_{H} 4.22) and H-9' β (δ_{H} 3.36), and of H-7' (δ_{H} 4.52) to H-9 α (δ_{H} 3.54) were observed, which indicated clearly that structure **A** is most appropriate for compound **1**. Further, the HMBC spectrum showed the presence of the long-range *W*-coupling correlation of H-9' α (δ_{H} 3.66) to C-1 (δ_{C} 128.4), which can exist only in conformation **E** rather than that **F**. In fact, only *cis*-8, 8' fused furofuran lignans have been found in nature. Further, there has been no literature report of a compound, either natural or synthetic, having the two hydroxy groups at C-8 and C-8' being in a *trans*-configuration. Nature has chosen a *cis*-8, 8' fusion rather than a *trans*-8, 8' fusion to form a furofuran lignan due to the steric restriction.²³ Accordingly, the structure of **1** was determined as 1 α ,3 α ,4 β ,6 α -1,4-bis(1,3-benzodioxol-5-yl)-furo[3,4-*c*]furan-3 α ,6 α -diol, and was given the trivial name vitexkarinol.

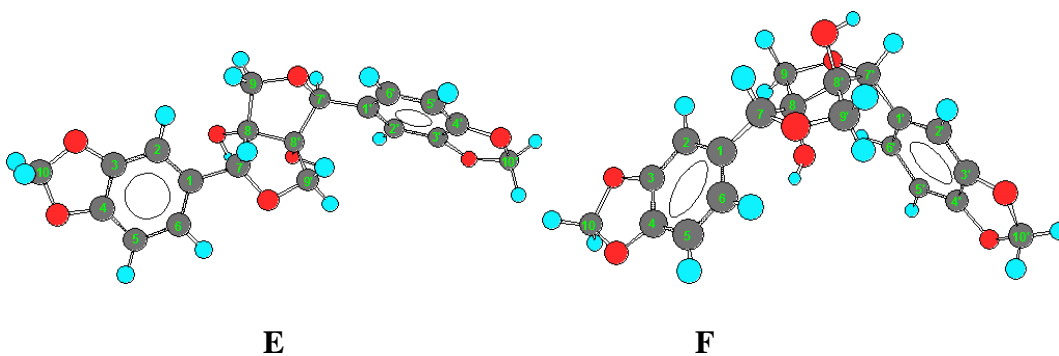


Figure 4. Conformational structures of **A** (left) and **B** (right).

Table 1. NMR Data (500 MHz, CDCl₃) for Vitexkarinol (**1**)

1			1		
position	δ_C , type	δ_H (J in Hz)	position	δ_C , type	δ_H (J in Hz)
1	128.4, C		1'	130.5, C	
2	107.4, CH	6.86 br s	2'	105.7, CH	6.93, br s
3	148.0, C		3'	147.5, C	
4	147.9, C		4'	146.9, C	
5	108.5, CH	6.79, d (8.1)	5'	108.1, CH	6.77, d (8.0)
6	120.1, CH	6.81, dd (8.2, 1.0)	6'	118.1, CH	6.90, dd (8.0, 0.8)
7	89.0, CH	4.54, br s	7'	85.7, CH	4.52, br s
8	85.8, C		8'	88.3, C	
9 α	75.06, CH ₂	3.54, d (9.8)	9'	75.12, CH ₂	3.36, d (10.8)
9 β		4.22, d (9.7)			3.66, d (10.8)
10	101.2 or 100.9, CH ₂	5.93, br s	10'	100.9 or 101.2, CH ₂	5.93, br s
OH-8		3.62 or 2.51, br s	OH-8'		2.51 or 3.62, br s

The structures of the known compounds were identified as neopaulowinin (**2**),²⁴ 3-(4-hydroxyphenyl)-1-(2, 4, 6-trimethoxyphenyl)-2-propen-1-one (**3**),²⁵ tsugafolin (**4**),²⁶ alpinetin (**5**),²⁷ aurantiamide,²⁸ aurantiamide acetate,²⁹ vemopolyanthofuran,³⁰ vomifoliol,^{31,32} dihydrovomifoliol,^{31,32} dehydrovomifoliol,³³ loliolide,³⁴ and isolololide,³⁵ by comparison of their spectroscopic data with those reported in the literature.

All compounds were isolated from different anti-HIV active fractions, and their

anti-HIV activity and cytotoxicity were measured. The chalcone (**3**) was found to be the most active, with an IC₅₀ value less than 15.2 μM, while its cytotoxicity to HOG. R5 cells at CC₅₀ gave a value of 24.4 μM. The two dehydroflavones (**4** and **5**) demonstrated weak anti-HIV activity with IC₅₀ values of 118 and 130 μM, respectively. Compound **4** showed slight toxicity to the HOG. R5 cells at 133 μM (24 % inhibition against the cell growth), whereas compound **5** was non-toxic to the cells at 148 μM. In addition, a chlorophyll enriched fraction containing pheophorbide *a*, was found to inhibit the replication of HIV-1 by 80% at a concentration of 10 μg/ml, which is consistent with our previous discovery that pheophorbide *a* is a potent anti-HIV agent.³⁶

Under a collaborative agreement with NIH NIAID, compounds **1** and **3** were selected for evaluation of potential activity against other viruses in a battery of 21 viral targets. Among these viral targets, only compounds **1** and **3** were shown to be slightly active against EBV (DNA hybridization assay using Akata cells) with EC₅₀ values of 67 μM (selective index = 1.2) and 15 μM (selective index = 3.5), respectively.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. IR spectra were run on a JASCO FT/IR-410 spectrometer, equipped with a Specac Silver Gate ATR system by applying a film on a germanium plate. 1D- and 2D-NMR spectra were recorded on a Bruker DRX-500 MHz NMR spectrometer. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals (CDCl₃; ¹H: 7.24 ppm; ¹³C: 77.00 ppm), and coupling constants (*J*) are

reported in Hz. All NMR experiments were obtained by using standard pulse sequences supplied by the vendor. HRTOFMS and MS/MS spectra were recorded on a Micromass QTOF-2 spectrometer. EIMS and HREIMS spectra were recorded on a Finnigan MAT 95 spectrometer. Column chromatography was carried out on silica gel (200-400 mesh, Natland International Corporation). Reversed-phase flash chromatography was accomplished with RP-18 silica gel (40-63 μm , EM Science), and reversed-phase HPLC was carried out on a Waters 600E Delivery System pump, equipped with a Waters 996 photodiode detector, and a GROM-Saphir 110 C₁₈ column (120 Å, 12 μm , 300 × 40 mm), or a Phenomenex, LUNA-C₁₈ column (12 μm , 250 × 50 mm). Thin-layer chromatography was performed on Whatman glass-backed plates coated with 0.25 mm layers of silica gel 60.

Plant Material. The initial collection (SV0477) of the leaves and twigs of *Vitex leptobotrys* was made in July, 1999 in the Bong Center of Cuc Phuong National Park, Ninh Binh Province, Vietnam (20° 21' 05" N; 105° 35' 39" E; 330 m alt), from a tree of 10 m in height. A larger amount of the plant sample (SVA0477), consisting of the same plant part (leaves and twigs) (3.6 kg), was re-collected from the same tree in March, 2001, for the current isolation work. Voucher specimens (*Soejarto & Cuong 10947*) are deposited at the Herbarium of Cuc Phuong National Park (CPNP) and at the Field Museum (F), Chicago, IL, USA.

Extraction and Isolation. The air-dried sample (3.6 kg) was extracted with CH₂Cl₂ at room temperature (×3). The resulting syrup CH₂Cl₂ extract (43.7 g) was separated by

silica gel column (1.0 kg) and developed by gradient elution with CHCl_3 and increasing concentrations of acetone to afford 25 fractions (F1-F25, each 1000 mL). The active fractions F5 and F6 (2.4 g) were combined and subjected to passage over a C_{18} reversed-phase (RP-18, 75 g) column. Elution of this column with 500 mL of MeOH- H_2O (9:1) yielded F26, which was then subjected to flash column chromatography on another C_{18} reversed-phase (RP-18, 130 g) column. Subsequent gradient elution with MeOH/ H_2O (1:9 to 9:1, each 500 mL; MeOH 100%, 1000 mL) yielded fractions F47-F56. The active fraction F53 (160 mg) was subjected to preparative HPLC separation on a Phenomenex LUNA- C_{18} column (solvent system: MeCN- H_2O , 60:40) to yield vitexkarinol (**1**, 93.4 mg), venopolyanthofuran (5.7 mg), neopaulowinin (**2**, 14.4 mg), aurantiamide acetate (2.1 mg). The MeOH solubles of F10 (1.6 g) were subjected to a C_{18} reversed-phase (RP-18, 75 g) column, and eluted with MeOH- H_2O , 8:2 (500 mL) to yield F29 (605 mg), which was further subjected to flash column chromatography on an additional C_{18} reversed-phase (RP-18, 30 g) column, eluting with a gradient of MeOH- H_2O (1:9 to 9:1, each 500 mL; MeOH 100%, 1000 mL). Among the resulting fractions F57-F66, the active fractions F60 (45 mg) and the combined fractions F62-F63 (150 mg) were respectively subjected to further preparative HPLC separation on a GROM-Suphir 110 C_{18} column to yield isololiolide (3.5 mg), dehydrovomifoliol (2.6 mg) and loliolide (19.6 mg) from fraction F60 (solvent system: MeCN- H_2O , 20:80), with tsugafolin (**4**, 12.0 mg), alpinetin (**5**, 3.8 mg), 3-(4-hydroxyphenyl)-1-(2,4,6-trimethoxyphenyl)-2-propen-1-one (**3**, 16.5 mg) and aurantiamide (3.6 mg) being obtained from pooled fraction F62-F63 (solvent system: MeCN- H_2O , 40:60). The MeOH-soluble portion of the combined fractions F14-F15 (907

mg) was subjected to flash column chromatography on a C₁₈ reversed-phase (RP-18, 30 g) column, and eluted with gradient mixture of MeOH-H₂O (2:8 to 9:1, each 500 mL; MeOH 100%, 1000 mL) to yield fractions F38-F46. The combined active fractions F38-F40 (38mg) were subjected to further preparative HPLC separation on the GROM-Suphir 110 C₁₈ column to yield dihydrovomifoliol (3.9 mg) and vomifoliol (8.4 mg) (solvent system: MeCN-H₂O, 15:85).

Vitexkarinol (I): colorless gum, $[\alpha]_D^{25} +32.8$, (*c* 4.8, CHCl₃); UV (MeOH) λ_{\max} (log ϵ) 236 (3.85), 286 (3.77) nm; IR (KBr) ν_{\max} 3477 (OH), 2868, 1504, 1491, 1444, 1254, 1243, 1149, 1128, 1103, 1038, 932, 756 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRFABMS *m/z* 409.0898 [M+Na]⁺ (calcd for C₂₀H₁₈O₈Na: *m/z* 409.0899), 369.0974 [M-H₂O]⁺ (calcd for C₂₀H₁₇O₇: *m/z* 369.0974), 351.0869 [M-2H₂O]⁺ (calcd for C₂₀H₁₅O₆: *m/z* 351.0869).

Anti-HIV Assay and Cytotoxicity Assays. Anti-HIV and cytotoxicity assays were performed in parallel using the green fluorescent protein (GFP)-based HOG-R5 reporter cell line that was constructed and developed specifically for quantitating HIV-1 infectivity. The system was validated and adapted as a moderately high-throughput procedure for screening natural products for anti-HIV activity in our laboratory.^{37,38} Briefly, a reporter cell line for quantitating HIV-1 replication was developed using HOS (human osteosarcoma) cells rendered susceptible to HIV-1 infection by the transfection of genes for CD4 and CCR5, the co-receptor utilized by macrophage-tropic (R5) HIV-1 isolates. This microtiter assay is based on the transactivation of a stably integrated HIV-1

LTR- GFP transcription unit. Upon HIV-1 entry into these HOS target cells, Tat expression increases the HIV LTR-directed transcription of the GFP gene as demonstrated by the increased fluorescence of detergent lysates of infected cells relative to that of uninfected controls. Procedures adopted for the assay were as described previously. The positive control compound used was 3TC (lamivudine), which had an IC₅₀ value of approximately 1.2 μM in the HOG.R5 system utilizing the assay conditions described above. This nucleoside reverse transcriptase inhibitor and the virus stock of HIV-1IIIB/H9 were obtained through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH.

Antiviral Activity Evaluated at NIAID. Under a collaborative agreement with NIAID, selected compounds were evaluated at the Southern Research Institute (Birmingham, AL, USA), for their antiviral potential against 21 viral targets: flu-A (Solomon Island/03/2006 H1N1, Wisconsin/67/2005 H3N2, and Vietnam/1203/2004H5N1 strains), flu B (Malaysia/2506/2004 strain), rhinovirus type-2 (HGP strain), adeno (65089/Chicago strain), parainfluenza (14702 strain), respiratory syncytial (A2 strain), SARS (Urbani strain), Rift Valley Fever (MP-12 strain), Tacribe (TRVL11573 strain), West Nile (New York isolate strain), hepatitis C, hepatitis B, human papilloma, measles (Chicago strain), herpes [Epstein-Barr, human cytomegalovirus, Varicella zoster, and herpes -1 and -2] viruses.

ASSOCIATED CONTENT

Supporting Information

Spectra of vitexkarinol (**1**); this material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

* E-mail: zhanghj@hkbu.edu.hk. Tel: +852 34112956. Fax: +852 34112461.

Notes

The authors declare no competing financial interest.

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Table of Contents (TOC)

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