Cytotoxic phenolic compounds isolated from the fruits of *Macaranga denticulata*

Tran Nguyen Vu Le, Bich Ngan Truong, Thi Phuong Le, Marc Litaudon, Dang Tran Thach, van Minh Chau, Huong Doan Thi Mai, Van Cuong Pham

► To cite this version:

Tran Nguyen Vu Le, Bich Ngan Truong, Thi Phuong Le, Marc Litaudon, Dang Tran Thach, et al.. Cytotoxic phenolic compounds isolated from the fruits of *Macaranga denticulata*. *Natural Product Research*, 2021, 35 (11), pp.1861-1868. 10.1080/14786419.2019.1639175 . hal-03354034

HAL Id: hal-03354034

<https://hal.science/hal-03354034>

Submitted on 27 Sep 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Cytotoxic phenolic compounds isolated from the fruits of *Macaranga denticulata*

Tran Nguyen Vu Le^{a,b}, Bich Ngan Truong^{a,b}, Thi Phuong Le^a, Marc Litaudon^c, Dang Thach Tran^d, Van Minh Chau^a, Huong Doan Thi Mai^{a,b,*} and Van Cuong Pham^{a,b,*}

^a*Advanced Center for Bioorganic Chemistry, Institute of Marine Biochemistry, Vietnam Academy of Science and Technology (VAST), 18, Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*

^b*Faculty of Chemistry, Graduate University of Science and Technology, VAST, Hanoi, Vietnam*

^c*Institut de Chimie des Substances Naturelles, CNRS-ICSN, UPR 2301, Université Paris-Saclay, 91198, Gif-sur-Yvette, France*

^d*Institute of Applied Science and Technology, University Industry Vinh, Vinh, Vietnam*

Address for correspondence

Assoc. Prof. Huong Doan Thi Mai and Assoc. Prof. Van Cuong Pham

Institute of Marine Biochemistry

Vietnam Academy of Science and Technology

18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam

Tel.: 8424 37564995

E-mail address: huongdm@imbc.vast.vn (Huong Doan Thi Mai);

phamvc@imbc.vast.vn (Van Cuong Pham)

ABSTRACT

A new modified geranylated flavonoid, 6-(8''-hydroxy-3'',8''-trimethyl-oct-2''-enyl)-kaempferol (**1**), along with seventeen known compounds (**2-18**) were isolated from the fruits of *Macaranga denticulata*. Their structures were established by spectral analysis, such as mass spectrometry, 1D-NMR, and 2D-NMR. Compounds **1-13** were evaluated for their cytotoxicity against seven cancer cell lines MCF-7, HepG2, Hep3B, Lu-1, Hela, KB, A549. The new geranylated flavonoid **1** showed a moderate cytotoxic activity against the A549 cell line with IC₅₀ value of 16.0 µM. Compound **9** showed the highest cytotoxic activities against KB, HepG2, Lu-1, and MCF7 cell lines with IC₅₀ values of 0.6, 0.8, 1.3, and 1.2 µM, respectively.

KEYWORDS : *Macaranga denticulata*; Euphorbiaceae; prenylated flavonoids;

1. Introduction

Macaranga is a large genus of the Euphorbiaceae family, consisting in more than 300 species found mainly in the southern part of Asia [1, 2]. In Vietnam, this genus comprises 13 different species. *Macaranga denticulata* Muell. Arg. (Euphorbiaceae) is a small to medium-sized tree. The roots were used in traditional medicine for treating icteric hepatitis (Fan et. al. 2015). The leaves or stem water decoctions can be used traditionally for washing wounds and drunk as tonic by women after childbirth [3, 4]. (Phupattanapong and Wongprasert 1987; Vo 2012) Previous studies on this species have resulted in the isolation of prenylated flavonoids from the leaves [5], stilbene-diterpene heterodimer and prenylated flavonoids from the frond [6], terpenoids from the root [7] and C-methylated and isoprenylated chalcones from the twigs and leaves [8-10]. As a part of our study in the search for new anticancer compounds from Vietnamese medicinal plants, the ethyl acetate extract of the fruits of *M. denticulata* was found to inhibit the growth of KB cancer cell line. In this paper, we report the isolation and structural elucidation of a new modified geranyl-type side chain substituted flavonoid, 6-(8''-hydroxy-3'',8''-trimethyl-oct-2''-enyl)-kaempferol (**1**) from the fruits of

M. denticulata along with 11 prenylated flavonoids (**2-12**), a prenylated stilbene (**13**), two diterpenoids (**14** and **15**), a sesquiterpenoid (**16**), and two triterpenoids (**17** and **18**) from the fruits of *Macaranga denticulata* Muell. Arg. (Euphorbiaceae). The cytotoxic activity of isolated compounds was also discussed.

2. Results and discussion

Compound **1** was isolated as a yellow powder and its molecular formula of $C_{25}H_{28}O_7$ was established by HRESIMS at m/z 439.1779 $[M-H]^-$ (calcd. 43.1757), requiring 12 unsaturation degrees. The FT-IR showed absorption bands at ν_{max} 3419, 1650, 1624, 1486 cm^{-1} indicating the presence of hydroxy, α,β -unsaturated carbonyl and aromatic ring functionalities, respectively. The UV absorption maximum at 349 and 257 nm was typical for a flavonol skeleton [9]. The presence of a substituted flavonol skeleton (more precisely substituted kaempferol) was suggested by 1H -NMR and ^{13}C -NMR (table 1). In the 1H NMR spectrum, the presence of an A_2B_2 system at δ_H 6.93 (2H, d, $J = 9.0$ Hz), 8.09 (2H, d, $J = 9.0$ Hz) and a singlet proton at δ_H 6.44 was observed at the aromatic region. Additionally, the appearance of 3 methyl groups at δ_H 1.16 (2 x CH_3) and 1.80 (CH_3), a benzylic methylene proton at δ_H 3.35, three methylene protons at δ_H 1.49, 1.80, 2.00, and a vinyl proton at δ_H 5.28, in the 1H NMR spectrum suggested the presence of a 8''-hydroxy-3'',8''-trimethyl-oct-2''-enyl moiety [11]. The analysis of ^{13}C -NMR data of **1** aided by HSQC revealed the presence of 25 carbons, including three methyls, four methylenes, six sp^2 methines, four oxygenated tertiary and six quaternary sp^2 carbons, one sp^3 oxygenated tertiary carbon and one carbonyl carbon. The chemical shifts of carbons at δ_C 71.5 (C-8''), 137.0 (C-3), 147.7 (C-2), 156.2 (C-9), 159.1 (C-5), 160.4 (C-4'), 163.4 (C-7) suggested their linkage to oxygen. The HMBC correlations of H-6'' (δ_H 1.49) with C-8'' (δ_C 71.5) and the correlations of methyl protons at δ_H 1.16 (CH_3 -9'' and 10'') with carbon at δ_C 71.5 (C-8''), 44.2 (C-7'') indicated the location of hydroxy group at C-8'' of geranyl chain. Furthermore, HMBC correlations of H-1'' (δ_H 3.45) with C-5 (δ_C 159.1), C-6 (δ_C 112.3), C-7 (δ_C 163.4) and which of H-2'' (δ_H 5.28) with C-6 (δ_C 112.3) determined the linkage of the modified geranyl-type side chain at C-6 of ring A. The double bond in the side chain for **1** was assigned as *E*, based on the 1H NMR and ^{13}C -NMR chemical shifts of the vinylic methyl group in 8''-hydroxy-3'',8''-trimethyl-oct-2''-enyl [11, 12]. Thus, the structure of new compound **1** was

identified as 6-(8''-hydroxy-3'',8''-trimethyl-oct-2''-enyl)-kaempferol and named 3'-dehydroxy-solophenol C (figure 1).

The known compounds were identified as denticulatain D (**2**) [9], bonannione A (**3**) [13, 14], diplacol (**4**) [14], macarangin (**5**) [5, 15], 3-*O*-methylmacarangin (**6**) [5, 15], 5,7,3',4'-tetrahydroxy-3-methoxy-6-geranylflavone (**7**) [9], 3,5,7,3',4'-pentahydroxy-6-geranylflavonol (**8**) [9], macarhizinoidin A (**9**) [16], robipseudin A (**10**) [17], denticulatain E (**11**) [9], 8-dimethylallylisakuranetin (**12**) [18], 4'-deprenylmappain (**13**) [19], deheiculatin H (**14**) [20], poilaneic acid (**15**) [21], derivative phaseic acid (**16**) [22], taraxerone (**17**) [23, 24], epitaraxerol (**18**) [25] by detailed analyses of their NMR and ESI-MS data and their comparison with reported values. Compounds **9**, **12**, **13**, **14**, **15** were isolated from *M. denticulata* for the first time. Compound **10**, **16** were isolated from *Macaranga* genus for the first time. *Macaranga denticulata* is phylogenetically very close to *Macaranga tanarius*. The two species that cohabitates in same biotopes are particularly difficult to discriminate in the field even in case of the presence of fruits or flowers. However, from a phytochemical point of view it should be noted that unlike *M. tanarius*, (ref Peresse et al . JNP 2017, 80, 2684-2691), no prenylated stilbene possessing a hexahydroxanthene moiety could be identified in *M. denticulata*.

Since prenylated flavonoid and prenylated stilbenes from *Macaranga* genus are reported to have potent cytotoxic activities [26, 27], the cytotoxic activities of compound **1-13** were evaluated against seven cancer cell lines: MCF-7 (human breast cancer cells), HepG-2 and Hep3B (human liver cancer cells), Lu-1 (human lung adenocarcinoma cells), Hela (human cervical cancer cells), KB (human epithelial carcinoma cells), A549 (human non-small cell lung cancer) by MTT-based colorimetric assay [28, 29]. The results showed that compound **1** showed moderate cytotoxic activity against A549 and Hela cell lines with IC₅₀ values of 16.0 and 36.9 µM, respectively. Compound **9** showed the highest cytotoxic activities against KB, HepG2, Lu-1, and MCF7 cell lines with IC₅₀ values of 0.6, 0.8, 1.3, and 1.2 µM, respectively. Compound **8** showed potent cytotoxic activity against KB cell line with an IC₅₀ value of 1.4 µM. Compound **3** showed selectively cytotoxic activity against the Hep3B cell line with an IC₅₀ value of 3.63 µM. Compound **5** showed a selective cytotoxic activity against the A549 cell line with an IC₅₀ value of 4.5 µM (Table 2).

3. Experimental

3.1. General experimental procedures

Melting points were recorded on a Buchi B-545 instrument (Ontario, Canada). Optical rotations were recorded on a Polax-2L polarimeter in CHCl₃ (ATAGO Co. Ltd., Tokyo, Japan). IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer (SpectraLab Scientific Inc., Ontario, Canada), and NMR spectra on a Bruker AM 500 MHz spectrometer (Bruker BioSpin AG, Fällanden, Switzerland) operating at 125.76 MHz for ¹³C NMR, and at 500.13 MHz for ¹H NMR. ¹H chemical shifts were referenced to CD₃OD at δ 3.31, while the ¹³C chemical shifts were referenced to the central peak at δ 49.0. The HMBC measurements were optimized to 7.0 Hz long-range couplings.. HR-ESI-MS were recorded on a FT-ICR 910-MS TQFTMS-7 T mass spectrometer (Agilent Technologies, Inc., California, USA).

3.2 Plant material

Fruits of *M. denticulata* were collected in Sa Pa, Lao Cai, Viet Nam on July 2015, and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources, VAST. A voucher specimen (VN-2497) was deposited at the Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology in Hanoi.

3.3 Extraction and isolation

Dry powdered fruits of *M. denticulata* (3.0 kg) was successively extracted with EtOAc (4 x 5 L) and then with methanol (3 x 5 L) at room temperature. The resulting EtOAc and MeOH extracts were evaporated under reduced pressure to give 330 g and 150 g of crude extracts, respectively. The ethyl acetate extract (330 g) of fruits of *M. denticulata* was subjected to a silica gel column chromatography (CC) and eluted with *n*-hexane/EtOAc gradient resulting in 20 fractions (F1-F20). Fraction 5 (2.5 g) was washed with *n*-hexane, the solid residue followed by recrystallization from acetone to yield compound **18** (150 mg) and the soluble crude was purified by CC on silica gel, eluting with *n*-hexane/acetone (97/3) provided compound **14** (20 mg). Fraction 7 (3.0 g) was washed with *n*-hexane, the solid residue obtained was subjected to column chromatography on silica gel, eluted with a mixture *n*-hexane/acetone (97/3) to yield compound **19** (36.0 mg). Fraction F11 (12 g) was separated by silica gel column chromatography, eluted with a mixture of *n*-

hexane/acetone (0 to 100% acetone in *n*-hexane) to give 12 subfractions. Subfraction 11.7 (0.8 g) was purified by column chromatography over silica gel, eluting with CH₂Cl₂/acetone (0 to 80% acetone in CH₂Cl₂) to obtain seven subfractions. Subfraction 11.7.4 (178 mg) was subjected to column chromatography on silica gel, eluted with a mixture CH₂Cl₂/acetone (95/5) to yield compound **9** (20.0 mg). Subfraction 11.7.6 (400 mg) was purified by column chromatography (CC) over silica gel, eluted with a mixture CH₂Cl₂/acetone (5 to 20% acetone in CH₂Cl₂) and then subjected on a Sephadex LH-20 column using a mixture of CH₂Cl₂/MeOH (1/9) to yield compound **16** (5.0 mg). Subfraction 11.9 (0.5 g) was washed with *n*-hexane/CH₂Cl₂ (9/1), the solid residue was recrystallized in EtOH, affording compound **12** (30.0 mg). Subfraction F11.11 (2.76 g) was separated on a silica gel column, eluted with CH₂Cl₂/EtOAc (5 to 50% EtOAc in CH₂Cl₂), then re-purified by Sephadex LH-20 column (100% MeOH) to give compound **3** (10.0 mg). Subfraction 11.12 (1.0 g) was purified by column chromatography over silica gel, eluting with CH₂Cl₂/acetone (0 to 100% acetone in CH₂Cl₂) to obtain five subfractions. Subfraction 11.12.4 (0.3 g) was further separated on a Sephadex column, eluted with MeOH and then purified on a silica gel, eluted with a mixture of CH₂Cl₂/acetone (5 to 10% acetone in CH₂Cl₂) to give compounds **5** (15 mg), **6** (5 mg), and **10** (18 mg). Fraction 17 (43 g) was chromatographed on silica gel column, eluting with a mixture of CH₂Cl₂/MeOH (0 to 80% MeOH in CH₂Cl₂) to give 13 subfractions. Subfraction F17.9 (2.88 g) was purified on a Sephadex LH-20 column, eluted with MeOH to obtain 7 subfractions F17.9.1-17.9.7. Subfraction F17.9.6 (0.33 g) was then purified on a silica gel, eluted with a mixture of CH₂Cl₂/MeOH (5 to 50% MeOH in CH₂Cl₂), followed by crystallization to yield compounds **8** (15 mg) and **13** (10.0 mg). Subfraction F17.10 (3.7 g) was separated by silica gel column chromatography, eluted with a mixture of CH₂Cl₂/MeOH gradient to give 7 subfractions. Subfraction F17.10.3 (437 mg) was purified by CC on Sephadex LH-20 (CH₂Cl₂/MeOH: 1/9), followed by CC on silica gel (0 to 70% acetone in CH₂Cl₂), to provide compounds **4** (13.0 mg), **7** (6.0 mg), and **15** (9.0 mg). Subfraction F17.10.4 was separated on a silica gel column, eluted with a mixture of CH₂Cl₂/acetone/MeOH (100/2/1) to yield compounds **1** (6.0 mg) and **2** (5.0 mg). The MeOH extract (150 g) was dissolved in 500 mL of acetone/MeOH (1/1), the soluble part was evaporated under reduced pressure to give 100 g of crude. This crude was subjected to a CC on silica gel (CH₂Cl₂/EtOH) to give 16 fractions (MF1-MF16).

Fraction MF10 (1.45 g) was purified on a Sephadex LH-20 column (100% MeOH), then purified by CC on silica gel column, eluted with a mixture of CH₂Cl₂/MeOH (5 to 50% MeOH in CH₂Cl₂) to yield compound **11** (6.0 mg).

3.3.1. 3'-dehydroxy-solophenol C (1)

Yellow powder mp. 160-161°C; Rf: 0.4 (CH Cl₃-acetone-MeOH, 2:0.2:0.1); IR (KBr) ν_{max} 3419, 1650, 1624, 1486, 1368, 1321, 1254, 1186, 1035, 905, 802 cm⁻¹; ¹H and ¹³C NMR spectral data, see Table 1; HR-ESIMS: m/z 439.1779 [M-H]⁻ (calcd for C₂₅H₂₇O₇, 439.1757).

3.4. Cytotoxic activity assay

The cytotoxicity assay was carried out in triplicate in a 96-well microtiter plates against 7 cancer cell lines: KB, HepG2, Lu-1, Hela, A549, MCF-7, Hep3B. An MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide] assay was used to measure the viability of cells after extract treatment. Cells were seeded in 96-well plates at a density of 1.0×10⁵ cells/mL. Cells were treated with various concentrations of essential oils (0.3, 1, 3, 10, and 30 µg/mL) and then incubated at 37 °C for 24 h in fresh RPMI1640 medium. Cells were subsequently incubated at 37 °C with MTT (0.5 mg/mL) for 4 h. After removal of supernatant, formazan crystals were dissolved in isopropanol and the optical density was measured at 570 nm. The IC₅₀ value was defined as the concentration of sample necessary to inhibit cell growth to 50% of the control. Ellipticine and camptothecine was used as a positive control.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

We gratefully acknowledge the International Associated Laboratory (LIA “NATPROCHEMLAB”) between the Centre National de la Recherche Scientifique (CNRS, ICSN, France) and the Vietnam Academy of Science and Technology (Institute of Marine Biochemistry, VAST, Vietnam), which supports the project and The Ministry of Science and Technology of Vietnam for financial support [Grant number DTĐLCN.14/16].

Supplemental data

HR-ESIMS, 1D- and 2D-NMR spectra of compounds **1** are available as Supporting Information.

References

- [1] S. Phommart, P. Sutthivaiyakit, N. Chimnoi, S. Ruchirawat and S. Sutthivaiyakit. *J. Nat. Prod.* **68**, 927-930 (2005).
- [2] G.L. Webster, *Annals of the Missouri Botanical Garden*, 3-32 (1994).
- [3] H.H. Pham. *The Flora of Vietnam*, Young Publisher, Ho Chi Minh City (1999).
- [4] V.C. Vo, In *Vietnamese Medicinal Plants Dictionary*, Science and Technology Publishing House, Hanoi, Vietnam (2004).
- [5] S. Sutthivaiyakit, S. Unganont, P. Sutthivaiyakit and A. Suksamrarn, *Tetrahedron* **58**, 3619-3622 (2002).
- [6] D.S. Yang, Z.L. Li, X. Wang, H. Yan, Y.P. Yang, H.R. Luo, K.C. Liu, W.L. Xiao and X.L. Li. *RSC Advances* **5**, 13886-13890 (2015).
- [7] J. Huang, W. Lu, X. Tan, G. Lu and Z. Huang, *Journal of Chinese medicinal materials* **38**, 1671-1673 (2015).
- [8] L.B. Zhang, C. Lei, L.X. Gao, J.Y. Li, J. Li and A.-J. Hou, *Nat. Prod. Bioprospect.* **6**, 25-30 (2016).
- [9] D.S. Yang, Z.L. Li, W.B. Peng, Y.P. Yang, X. Wang, K.C. Liu, X.L. Li and W.L. Xiao, *Fitoterapia*, **103**, 165-170 (2015).
- [10] C. Lei, L.B. Zhang, J. Yang, L.X. Gao, J.Y. Li, J. Li and A.J. Hou, *Tetrahedron Lett.* **57**, 5475-5478 (2016).
- [11] S. Inui, T. Hosoya, Y. Shimamura, S. Masuda, T. Ogawa, H. Kobayashi, K. Shirafuji, R.T. Moli, I. Kozono and K. Shin-ya. *J. Agric. Food. Chem.* **60**, 11765-11770 (2012).
- [12] Y. Hu and J.B. MacMillan. *Org Lett.* **13**, 6580-6583 (2011).
- [13] B.J. Yoder. Isolation and structure elucidation of cytotoxic natural products from the rainforests of Madagascar and Suriname. Virginia Tech (2005)
- [14] W.R. Phillips, N.J. Baj, A.L. Gunatilaka and D.G. Kingston, *J. Nat. Prod.* **59**, 495-497 (1996).
- [15] E. Hnawia, O. Thoison, F. Guéritte-Voegelein, D. Bourret and T. Sévenet, *Phytochemistry* **29**, 2367-2368 (1990).
- [16] M. Tanjung, D. Mujahidin, E.H. Hakim, A. Darmawan and Y.M. Syah, *Nat. Prod. Commun.* **5**, 1209-1211 (2010).
- [17] L.B. Zhang, J.L. Lv and H. Zhang, *Nat. Prod. Commun.* **8**, 335-336 (2013).
- [18] R. Chen, X. Liu, J. Zou, Y. Yin, B. Ou, J. Li, R. Wang, D. Xie, P. Zhang and J. Dai, *Adv. Synth. Catal.* **355**, 1817-1828 (2013).
- [19] S. Almutairi, B. Eapen, S.M. Chundi, A. Akhalil, W. Siheri, C. Clements, J. Fearnley, D.G. Watson and R. Edrada-Ebel, *Phytochem. Lett.* **10**, 35-39 (2014).
- [20] W.Y. Qi, Y. Shen, Y. Wu, Y. Leng, K. Gao and J.M. Yue, *Phytochemistry*, **136**, 101-107 (2017).
- [21] N. Nina, C. Quispe, F. Jiménez-Aspee, C. Theoduloz, G.E. Feresín, B. Lima, E. Leiva and G. Schmeda-Hirschmann, *Molecules* **20**, 18144-18167 (2015).
- [22] H. Kikuzaki, S.I. Kayano, N. Fukutsuka, A. Aoki, K. Kasamatsu, Y. Yamasaki, T. Mitani and N. Nakatani, *J. Agric. Food. Chem.* **52**, 344-349 (2004).
- [23] N. Sakurai, Y. Yaguchi and T. Inoue. *Phytochemistry* **26**, 217-219 (1986).

- [24] L.O.A. Manguro, J.O. Midiwo and W. Kraus, *Planta Med.*, **63**, 290-290 (1997).
- [25] V.K. Phan, V.M. Chau, T.H. Hoang, H.N. Nguyen, J.J. Lee and Y.H. Kim, *Arch, Pharm, Res.* **27**, 1109-1113 (2004).
- [26] J.J. Magadula. *J. Med. Plant. Res.* **8**, 489-503 (2014).
- [27] T. Peresse, G.l. Jézéquel, P.M. Allard, V.C. Pham, D.T. Huong, F. Blanchard, J. Bignon, H. Lévaïque, J.L. Wolfender and M. Litaudon. *J. Nat. Prod.* **80**, 2684-2691 (2017).
- [28] T. Mosmann, *J. Immunol. Methods*, **65**, 55-63 (1983).
- [29] M.V. Berridge, P.M. Herst and A.S. Tan, *Biotechnol. Annu. Rev.* **11**, 127-152 (2005).

Fan QF, Zheng JY, Song QS, Na Z, Hu HB. 2015. Chemical Constituents of the roots of *Macaranga denticulata*. *Chem Nat Compd.* 51:586–587.

L. Phupattanapong and T. Wongprasert, *Thai Medicinal Plants*, Chutima, Bangkok, 1987, part 5, p. 687.

Figure 1. Structures of compounds **1-18** from *M. denticulata*.

Table 1. ^1H and ^{13}C NMR spectral data of compounds **1** (^1H : 500 MHz and ^{13}C : 125 MHz).

Position	δ_{C}	δ_{H} (J in Hz)	Position	δ_{C}	δ_{H} (J in Hz)
2	147.7		4'	160.4	
3	137.0		1"	22.1	3.35 d (7.0)
4	177.3		2"	123.7	5.28 t (6.5)
5	159.1		3"	135.8	
6	112.3		4"	16.1	1.80 s
7	163.4		5"	41.3	2.0 t (7.5)
8	93.7	6.44 s	6"	23.6	1.49 m
9	156.2		7"	44.2	1.40 m
10	104.4		8"	71.5	
1'	123.9		9"	29.2	1.16 s
2',6'	130.6	8.09 d (9.0)	10"	29.2	1.16 s
3',5'	116.3	6.93 d (9.0)			
Measured in CD_3OD

Figure 2. Key HMBC correlations of compound 1.

Table 2. Cytotoxic activity of compounds **1-13** against seven cancer cell lines

Compound	IC ₅₀ values (μM)						
	KB	HepG2	Lu-1	MCF7	Hep3B	A549	Hela
1	>100	>100	>100	>100	62.8 ± 2.2	16.0 ± 0.2	36.9 ± 1.9
2	>100	>100	>100	>100	>100	>100	>100
3	37.2 ± 0.6	38.8 ± 0.2	38.7 ± 0.7	36.4 ± 2.2	3.6 ± 0.3	7.9 ± 0.9	15.9 ± 0.5
4	49.1 ± 1.7	53.1 ± 0.2	45.8 ± 1.9	10.7 ± 1.3	>100	>100	>100
5	41.7 ± 0.5	36.3 ± 0.2	33.1 ± 2.1	27.4 ± 1.3	14.4 ± 1.9	4.5 ± 0.5	7.8 ± 0.3
6	>100	>100	>100	>100	>100	>100	>100
7	46.9 ± 0.4	95.7 ± 6.1	81.1 ± 6.2	81.7 ± 2.1	>100	>100	>100
8	1.4 ± 0.1	7.2 ± 0.8	7.9 ± 0.1	1.3 ± 0.1	9.5 ± 0.4	3.4 ± 0.6	8.7 ± 0.4
9	0.6 ± 0.1	0.8 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	3.7 ± 0.5	4.5 ± 0.3	7.6 ± 0.8
10	29.3 ± 1.4	20.8 ± 1.5	28.3 ± 1.7	26.0 ± 2.1	61.7 ± 2.1	8.1 ± 1.1	9.8 ± 0.9
11	>100	>100	>100	>100	NT	NT	NT
12	>100	>100	>100	>100	NT	NT	NT
13	42.7 ± 0.1	34.9 ± 0.8	28.7 ± 1.3	28.2 ± 2.5	9.6 ± 0.7	7.6 ± 0.9	13.5 ± 0.4
Ellipticine	1.1 ± 0.1	0.85 ± 0.07	1.3 ± 0.1	1.4 ± 0.8	-	-	-
Camptothecin	-	-	-	-	0.12 ± 0.01	1.6 ± 0.1	2.9 ± 0.2

NT: Not tested