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# Cytotoxic Geranyl Stilbenes from *Macaranga schweinfurthii*

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Three novel geranyl stilbenes, schweinfurthins A, B, and C (**1**, **2**, and **3**), were isolated from the Cameroonian plant *Macaranga schweinfurthii* (Euphorbiaceae) and their structures determined by NMR and mass spectral methods. The cytotoxicity profile of the schweinfurthins tested in the NCI 60-cell screen was similar to that of the stelletins and cephalostatins, suggesting that these structurally diverse natural products may share similar mechanisms of cytotoxicity.



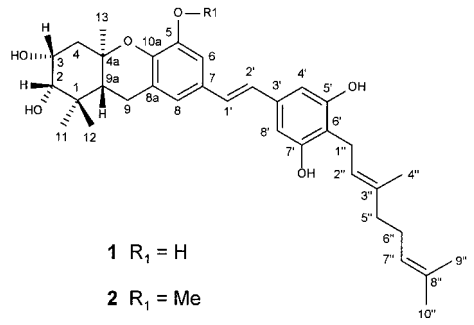
The genus *Macaranga* is one of the largest genera of the Euphorbiaceae, with approximately 300 species.[1] Previously reported compounds from the genus include a prenyl stilbene, vedelianin[2] and a geranyl flavonol[3] from *M. vedeliana*, antibacterial prenylated flavanones from *M. pleiostemona*,[4] chromenoflavones from *M. indica*,[5] and a diterpene from *M. tanarius*.[6] A number of species of *Macaranga* are substantial sources of hydrolyzable tannins.[7] No phytochemistry has been previously reported on *M. schweinfurthii*, and none of the above-cited compounds is documented to be cytotoxic. Our preliminary testing of *Macaranga* extracts available from the NCI repository found 11 samples from eight species of *Macaranga*, including *M. schweinfurthii*, to be devoid of phorbol ester bioactivity.[8,9]

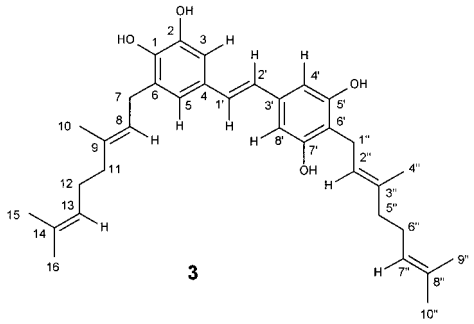
For the present study we selected an organic extract of *M. schweinfurthii* Pax based upon its prominent cytotoxicity toward several human tumor cell lines in the NCI panel,[10,11] notably the CNS tumor-derived lines SF-295 and SF-539. Here we describe the bioassay-guided isolation and structure elucidation of the compounds responsible for this cytotoxicity.

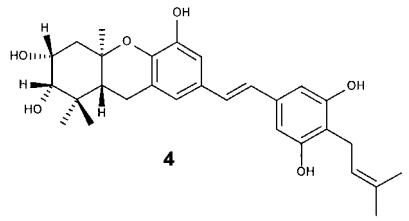
## Results and Discussion

Batch elution from diol bonded-phase media, Sephadex LH-20 permeation, C-18 vacuum liquid chromatography, and C-18 HPLC led to compounds **1** and **2** as the major cytotoxic constituents. Compound **3** was found as an inactive major congener.

Compound **1** was an optically active yellow glass $[\alpha]_D$ +51.8° with a molecular formula of $C_{34}H_{44}O_6$, as determined by HRFABMS. The UV maximum at 331 nm was consistent with a stilbene such as vedelianin,[2] and the $^1H$ and $^{13}C$ NMR spectra of **1** (Table 1) shared many features with this compound. The molecular formula of compound **1** differed by $C_5H_8$ from vedelianin (**4**), consistent with the presence of an additional prenyl group. HMQC and HMBC spectra confirmed that the planar structure of **1** was otherwise identical to vedelianin, and HMBC correlations between a signal at $\delta$ 2.05 (H-6″) and a methylene $^{13}C$ resonance at $\delta$ 40.9 (C-5″), as well as $\delta$ 134.8 ppm (C-3″), established the point of substitution for the additional prenyl group. The congruency of chemical shifts and scalar couplings in the cyclohexyl ring and similar sign and magnitude of optical rotations indicated that **1** possessed the same relative stereochemistry as **4**.




Compound **2** had the formula $C_{35}H_{46}O_6$ by HRFABMS, differing from **1** by an additional $CH_2$. This was also evident in the $^1H$ NMR (Table 2) by presence of a 3H singlet at $\delta$ 3.83 and a $^{13}C$ NMR resonance at $\delta$ 56.4. An HMBC correlation from this methyl group to the resonance at $\delta$ 150.1 placed the methoxyl group at C-5, which was shifted 3 ppm compared to compound **1**. Further HMBC correlations for **2** (data not shown) supported the assigned structure.

Schweinfurthin C (**3**) had the molecular formula $C_{34}H_{44}O_4$ by HRFABMS. The absence of $^{13}C$ NMR resonances between 70 and 80 ppm (Table 3) indicated that this compound lacked the vicinal diol functionality of compounds **1** and **2**. There were six methyl singlets in the $^1H$ NMR spectrum (from $\delta$ 1.55 to $\delta$ 1.75) and four vinyl triplets.

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**Table 1.** $^{13}$C NMR Data for **1**, **2**, and **4** ($\delta$ in ppm, $CD_3OD$, 125 MHz)

| carbon no. | $^{13}$C shift **1** | $^{13}$C shift **2**, DEPT multiplicity | $^{13}$C shift **4**[4] | HMQC to $^1$H for **2** |
|---|---|---|---|---|
| 1 | 39.1 | 39.1, s | 39.0 | |
| 2 | 78.8 | 78.7, d | 78.7 | 3.30 |
| 3 | 71.7 | 71.7, d | 71.7 | 4.14 |
| 4 | 44.6 | 44.7, t | 44.5 | 2.34, 1.94 |
| 4a | 78.2 | 78.0, s | 78.0 | |
| 5 | 147.0 | 150.1, s | 146.8 | |
| 6 | 111.1 | 108.3, d | 111.0 | 6.91 |
| 7 | 130.8 | 130.6, s | 130.7 | |
| 8 | 120.5 | 121.7, d | 120.5 | 6.84 |
| 8a | 124.2 | 124.3, s | 124.1 | |
| 9 | 23.9 | 23.9, t | 23.8 | 2.75 |
| 9a | 48.8 | 48.6, d | 48.6 | 1.74 |
| 10a | 137.6 | 137.5, s | 137.6 | |
| 11 | 16.3 | 16.2, q | 16.2 | 1.76 |
| 12 | 29.4 | 29.3, q | 29.3 | 1.10 |
| 13 | 22.0 | 21.9, q | 22.0 | 1.40 |
| 1′ | 128.7 | 128.5, d | 128.8 | 6.87 |
| 2′ | 127.4 | 127.6, d | 127.3 | 6.77 |
| 3′ | 141.9 | 143.3, s | 141.8 | |
| 4′, 8′ | 105.7 × 2 | 105.8 × 2, d | 105.9 | 6.47 |
| 5′, 7′ | 157.2 | 157.2 × 2, s | 157.1 | |
| 6′ | 115.9 | 115.9, s | 115.9 | |
| 1″ | 23.2 | 23.2, t | 23.3 | 3.30 |
| 2″ | 124.6 | 124.5, d | 124.5 | 5.25 |
| 3″ | 134.9 | 134.8, s | 131.3 | |
| 4″ | 13.5 | 16.5, q | 25.9 | 1.05 |
| 5″ | 40.9 | 40.9, t | 17.9 | 1.94 |
| 6″ | 27.8 | 27.7, t | | 2.05 |
| 7″ | 125.6 | 125.5, d | | 5.07 |
| 8″ | 131.9 | 131.9, s | | |
| 9″ | 17.7 | 17.7, q | | 1.56 |
| 10″ | 25.8 | 25.8, q | | 1.62 |
| MeO-5 | | 56.4, q | | 3.83 |

**Table 2.** $^1$H NMR of Schweinfurthin B (**2**) ($CD_3OD$, 500 MHz)

| proton no. | COSY to $^1$H | difference NOE to $^1$H |
|---|---|---|
| 2 | 4.14 | |
| 3 | 3.30, 2.34, 1.94 | 3.30, 2.34, 1.94 |
| 4 | 1.94 | 4.14, 1.94, 1.40 |
| 4a | 2.34 | |
| 5-MeO− | | |
| 6 | 6.83 | |
| 8 | 6.91 | |
| 9 | 1.74 | |
| 9a | 2.75 | |
| 11 | | |
| 12 | | |
| 13 | | |
| 1′ | 6.77 | |
| 2′ | 6.87 | |
| 4′, 8′ | | |
| 1″ | 5.25 | |
| 2″ | 3.30 | 3.30, 1.94, 2.05 |
| 4″ | | |
| 5″ | 2.05 | |
| 6″ | 1.94 | |
| 7″ | 2.05, 1.56, 1.62 | 1.62 |
| 9″ | | |
| 10″ | | |

These observations were accountable to a stilbene with two geranyl chains and four phenolic groups. Although the NMR data indicated that one side chain was attached in the same fashion as in **1** and **2**, the other geranyl group was different. The second geranyl substituent was placed by the HMBC correlations of the aromatic proton at $\delta$ 6.67 (H-5) to the methylene carbon resonance at $\delta$ 29.1 (C-7) and the phenolic carbon at $\delta$ 144.2 (C-1). The aromatic ortho-coupled proton ($\delta$ 6.81, H-3) was correlated to the phenolic carbon resonances at $\delta$ 144.2 (C-1) and $\delta$ 146.1 (C-2), establishing this ring as a 3,5-disubstituted 1,2-catechol.

**Table 3.** Results of *In Vitro* Time-Course Experiments with Schweinfurthins A (**1**) and B (**2**) in Sensitive (SF-295) and Resistant (A549) Cell Lines[a]

| compound | **1** | | **2** | |
|---|---|---|---|---|
| protocol | A549 | SF-295 | A549 | SF-295 |
| 1 h | 43 | 47 | >100 | >100 |
| 1 h washout | 20 | 0.06 | 80 | 2.9 |
| 48 h | 3.7 | <0.00001 | 7.1 | 0.009 |

[a] Values are $IC_{50}$ in $\mu$g/mL.

The purified compounds were evaluated in an in vitro time-course experiment using SF-295 and a resistant cell line, A-549. A 1-h treatment with compounds **1** and **2** led to negligible cytotoxicity, indicating that the compounds were not cytotoxic through a rapid mechanism such as membrane lysis. A 1-h treatment followed by compound washout and evaluation at 48-h demonstrated a modest differential cytotoxicity for each compound, while continuous 48 h treatment with the compounds generated a robust differential (Table 3).

Compounds **1** and **2** were tested in the 60-cell line human tumor cancer screen.[10] Schweinfurthin A (**1**) showed a mean panel $GI_{50}$ of 0.36 $\mu$M, while schweinfurthin B (**2**) was slightly less potent, giving a mean panel $GI_{50}$ of 0.81 $\mu$M. The brain tumor (CNS) subpanel was the most sensitive to both compounds, while the ovarian cancer cell lines were uniformly resistant. The most sensitive cell line was the CNS line SF-295, for which schweinfurthin A (**1**) gave a $GI_{50}$ of 11 nM and a TGI of 52 nM. Other sensitive lines included leukemia (CEM, HL-60, MOLT-4, and RMPI-8226) and lung (HOP-62), CNS (SF-539 and SNB-75), renal (786−0, RXF-393, and UO-31), and breast (HS 578T) cancers. The differential cytotoxicity profiles are further documented in the Experimental Section.

The NCI 60-cell mean-graph cytotoxicity profiles showed little or no resemblance to those of any of the profiles in the NCI's standard agents database.[12] However, when analyzed at the $GI_{50}$ and TGI levels of response using the Compare program,[12,13] the schweinfurthins showed relatively high correlations to stellettin A[14] (e.g., 0.75, 0.75) and cephalostatin 1[15] (e.g., 0.59, 0.66). The cell lines sensitive to these compounds differ substantially in many known characteristics including in vitro doubling time, DNA repair phenotype, and MDR status. No common biochemical feature of these lines is apparent which could explain their particular sensitivity to these compounds. These results suggest that the schweinfurthins may share with the stellettins and cephalostatins similar mechanism(s) of cytotoxicity.

## Experimental Section

**General Experimental Procedures.** NMR spectra were acquired on a Varian VXR-500 spectrometer with an inverse detection probe. Optical rotations were obtained on a Perkin−Elmer model 204 polarimeter. UV spectra were acquired using a Beckman DU640 spectrophotometer, while IR spectra were obtained on a Perkin−Elmer Spectrum 2000 FT-IR spectrophotometer. FABMS were obtained on a JEOL SX102 mass spectrometer operated at an accelerating voltage of 10 kV. Samples were desorbed from a nitrobenzyl alcohol matrix using 6 keV xenon atoms. Mass measurements in FAB were performed at 10 000 resolution using electric field scans and the matrix ions as the reference material.

**Plant Material.** Leaves of *Macaranga schweinfurthii* Pax were collected by D. W. Thomas (*Thomas 6771*, voucher in

Missouri Botanical Garden, collection Q66P364) in the vicinity of Mundemba, Ndian Division, Korup National Park, Cameroon, in March 1987.

**Cytotoxicity Bioassay.** Two cell lines from the NCI CNS screening panel (SF-295 and SF-539) were chosen for a two-day cytotoxicity assay[16] to monitor fractionation.

**Isolation.** Ground, dry leaves (425 g) were extracted with $CH_2Cl_2$−MeOH (1:1 v/v) and then MeOH; the solvent was evaporated to yield 22.4 g of organic extract. Of this extract 5.0 g was coated on 25 g of diol media (YMC) and eluted with 500 mL each of hexane, $CH_2Cl_2$, EtOAc, $Me_2CO$, and MeOH in sequence. The EtOAc fraction (1.55 g) contained ca. 94% of the cytotoxicity and was further fractionated by permeation though Sephadex LH-20 using $CH_2Cl_2$−MeOH (1:1 v/v). The fourth of five fractions collected (0.51 g) contained ca. 99% of the cytotoxicity. It was dissolved in MeOH, coated on 10 g of flash grade $C_{18}$ media (YMC), and eluted with 200 mL each of 50% MeOH, 70% MeOH, 80% MeOH, 90% MeOH, and MeOH. The 70% MeOH fraction was the most cytotoxic. HPLC of this fraction in 25-mg aliquots on $C_{18}$ (21 × 250 mm, 60 Å, Rainin Dynamax column) using a linear 70−100% MeOH gradient yielded 50 mg of schweinfurthin A (**1**), 38 mg of schweinfurthin B (**2**), and 25 mg of schweinfurthin C (**3**).

**Compound Data. Schweinfurthin A (1):** NSC#696119; yellowish solid; $[\alpha]_D$ +51.8° (*c* 2.0, EtOH); UV (EtOH) $\lambda_{max}$ 224 nm (log $\epsilon$ 4.48), 331 nm (4.58); IR (film) 3419 (br), 1710, 1592, 1496, 1428, 1374, 1258, 1046, 959, 930 $cm^{-1}$; $^1H$ NMR 6.82 (d, 1H, *J* = 16 Hz, H-1′), 6.80 (d, 1H, 2, H-6), 6.71 (d, 1H, 16, H-2′), 6.69 (d, 1H, 2, H-8), 6.46 (s, 2H, H-4′, 8′), 5.25 (tq, 1H, 7.1, 1.2, H-2″), 5.07 (t pentet, 1H, 7.1, 1.4, H-7″), 4.13 (d, 1H, 2.4, H-3), 3.35 (m, 4H, H-2, 9a, 1″), 2.71 (m, 2H, H-9), 2.35 (d, 1H, 13, H-4a), 2.04 (t, 2H, 7.3, H-6″), 1.95 (t, 2H, 7.3, H-5″), 1.94 (m, 1H, H-4), 1.76 (s, 3H, H-11), 1.62 (s, 3H, H-10″), 1.56 (s, 3H, H-9″), 1.40 (s, 3H, H-13), 1.08 (s, 3H, H-12), 1.07 (s, 3H, H-4″); $^{13}C$ NMR, see Table 1; HRFABMS (noba, positive mode) $M^+$ 548.3113 (calcd for $C_{34}H_{44}O_6$ 548.3138).

**Schweinfurthin B (2):** NSC#696118, yellowish solid; $[\alpha]_D$ +44.7° (*c* 1.0, EtOH), UV (EtOH) $\lambda_{max}$ 223 nm (log $\epsilon$ 4.44), 331 nm (4.52), IR (film) 3433 (br) 1708, 1588, 1493, 1431, 1374, 1257, 1156, 1086, 1043, 956, 909, 849 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 6.91 (1H d, *J* = 2.0 Hz, H-6), 6.87 (1H d, *J* = 16 Hz, H-1′), 6.83 (1H d, *J* = 2.0 Hz, H-8), 6.77 (1H d, *J* = 16 Hz, H-2′), 6.47 (2H br s, H-4′ and H-8′), 5.25 (1H tq, *J* = 7.2, 1.2 Hz, H-2″), 5.07 (1H t pentet, *J* = 7.2, 1.4 Hz, H-7″), 4.14 (1H q, *J* = 3.4 Hz, H-3), 3.83 (3H s, 5-MeO-), 3.30 (obscured by solvent, H-2 and H-1″), 2.75 (2H m, H-9), 2.34 (1H dd, *J* = 13.9, 3.3 Hz, H-4), 2.05 (2H m, H-6″), 1.94 (3H m, H-4a and H-5″), 1.76 (3H s, H-11), 1.74 (1H m, H-9a), 1.62 (3H s, H-10″), 1.56 (3H s, H9″), 1.40 (3H s, H-13), 1.10 (3H s, H-12), 1.08 (3H s, H-4″); $^{13}C$ NMR, see Table 1; FABMS (noba, positive mode) 562, 532, 460, 407, 307, 289; HRFABMS (noba, positive mode) $M^+$ 562.3308 (calcd for $C_{35}H_{46}O_6$ 562.3294).

**Schweinfurthin C (3):** NSC#698298; UV $\lambda_{max}$ 330 nm (log $\epsilon$ 4.03), EtOH, IR 3423 (br), 1590, 1499, 1440, 1302, 1036, 958, 849 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 6.81 (1H m, *J* = 2.3 Hz, H-3), 6.77 (1H d, *J* = 16 Hz, H-1′), 6.67 (1H m, *J* = 6.3, 2.2 Hz, H-5), 6.63 (1H d, *J* = 16 Hz, H-2′), 6.43 (2H s, H-4′ and H-8′), 5.33 (1H t, *J* = 7.4, H-8), 5.24 (1H t, *J* = 7.4 Hz, H-2″), 5.11 (1H t, *J* = 7.2, H-13), 5.07 (1H t, *J* = 7 Hz, H-7″), 3.34 (obscured by solvent, H-7), 3.27 (obscured by solvent, H-1″), 2.11 (2H t, *J* = 7.8 Hz, H-12[a]), 2.04 (4H t, *J* = 7.8 Hz, H-11 and H-6″[a]), 1.93 (2H t, *J* = 7.2 Hz, H-5″), 1.75 (3H s, H-4″), 1.72 (3H s, H-10), 1.64 (3H s, H-16[c]), 1.62 (3H s, H-10″[c]), 1.58 (3H s, H-15 [b]), 1.56 (3H s, H-9″ [b]); $^{13}C$ NMR ($CD_3OD$, 125 MHz), $\delta$ 157.2 (2C s, C-5′ and C-7′), 146.1 (s, C-2), 144.2 (s, C-1), 137.7 (s, C-3′), 136.6 (s, C-9), 134.8 (s, C-3″), 132.2 (s, C-14), 132.0 (s, C-8″), 130.3 (s, C-4), 129.6 (s, C-6), 129.0 (d, C-1′), 127.0 (d, C-2′), 125.5 (d, C-7″), 125.3 (d, C-13), 124.6 (d, C-2″), 124.1 (d, C-8), 120.6 (d, C-5), 115.8 (s, C-6′), 111.0 (d, C-3), 105.7 (2C d, C-4′ and C-8′), 41.0 (t, C-5″), 40.9 (t, C-11), 29.1 (t, C-7), 27.8 (t, C-6″[a]), 27.7 (t, C-12[a]), 25.9 (q, C-10″[c]), 25.8 (q, C16[c]), 23.2 (t, C-1″), 17.8 (q, C-9″[b]), 17.7 (q, C-15[b]), 16.3 (q, C-4″), 16.2 (q, C-10) (assignment of $^1H$ and $^{13}C$ signals with the same superscript may be reversed); FABMS (noba, positive mode) 516, 460, 393, 307, 289, 165; HRFABMS 516.3242 (calcd for $C_{34}H_{44}O_4$ 516.3240).

**NCI 60-Cell Cancer Assay Data.**[17] The tumor cell line subpanels are identified as follows: I (leukemia); II (lung, nonsmall-cell); III (colon); IV (CNS); V (melanoma); VI (ovarian); VII (renal); VIII (prostate); IX (breast). The subpanel and individual cell-line identifiers are given, along with the corresponding negative log $GI_{50}$, TGI, and $LC_{50}$ values (molar), respectively, for: schweinfurthin A (**1**) [I] CCRF−CEM (8.00, 5.68, 4.13), HL-60 (7.80, 6.89, 4.41), K-562 (7.19, 4.85, 4.14), MOLT-4 (7.82, 5.89, 4.24), RPMI-8226 (8.00, 7.68, 4.12), SR (7.15, 4.74, 4.13) [II] A549 (6.85,4.85, 4.39), EKVX (6.80, 4.82, 4.36), HOP-62 (6.92, 4.82, 4.32), HOP-92 (5.59, 4.82, 4.33), NCI−H226 (5.35, 4.80, 4.15), NCI−H23 (5.49, 4.74, 4.29), NCI−H322M (5.21, 4.68, 4.32), NCI−H460 (7.89, 4.92, 4.41), NCI−H522 (5.59, 5.00, 4.57) [III] COLO205 (5.96, 5.55, 5.15), HCC-2998 (6.30, 5.01, 4.48), HCT-116 (7.28, 4.85, 4.39), HCT-15 (5.74, 5.22, 4.59), HT29 (6.51, 5.62, 5.26), KM12 (5.82, 4.85, 4.52), SW-620 (6.59, 4.74, 4.35) [IV] SF-268 (5.62, 4.68, 4.13), SF-295 (7.96, 7.28, 4.77), SF-539 (8.00, 5.77, 5.09), SNB-19 (6.59, 4.70, 4.31), SNB-75 (7.82, 6.42, 4.30), U251 (7.60, 4.64, 4.31) [V] LOX IMVI (7.42, 4.77, 4.41), MALME−3M (5.37, 4.70, 4.27), M14 (7.80, 6.49, 5.57), SK-MEL-2 (5.77, 4.89, 4.37), SK-MEL-28 (5.34, 4.62, 4.22), SK-MEL-5 (7.04, 5.55, 4.92), UACC-257 (5.37, 4.74, 4.36), UACC-62 (6.96, 5.74, 5.20) [VI] IGROV1 (5.89, 4.96, 4.46), OVCAR-3 (5.51, 5.10, 4.66), OVCAR-4 (5.37, 4.62, 4.09), OVCAR-5 (5.19, 4.70, 4.34), OVCAR-8 (5.29, 4.70, 4.24), SK−OV-3 (5.57, 4.80, 4.40) [VII] 786−0 (8.00, 5.52, 4.72), A498 (5.38, 4.64, 4.21), ACHN (5.68, 4.80, 4.40), CAKI-1 (6.89, 4.72, 4.25), RXF-393 (8.00, 5.68, 4.26), SN12C (5.16, 4.60, 4.21), TK-10 (5.59, 4.77, 4.38), UO-31 (8.00, 6.68, 5.44) [VIII] PC-3 (6.77, 4.89, 4.44), DU-145 (5.92, 4.82, 4.27) [IX] MCF7 (7.57, 5.09, 4.07), MCF7/ADR−RES (5.42, 4.89, 4.38), MDA-MB-231 (5.38, 4.60, 4.15), HS 578T (8.00, 6.12, 4.06), MDA-MB-435 (5.42, 4.48, 4.13), MDA-N (5.55, 4.59, 4.21), BT-549 (4.89, 4.49, 4.13), T-47D (5.49, 4.66, 4.01).

Schweinfurthin B (**2**) [I] CCRF−CEM (6.64,5.20, 4.00), HL-60 (7.43, 5.89, 4.00), K-562 (6.46, 5.21, 4.44), MOLT-4 (7.32, 5.28, 4.96), RPMI-8226 (7.82, 6.96, 4.92), SR (6.59, 4.92, 4.23) [II] A549 (6.47,4.85, 4.41), EKVX (6.03, 4.85, 4.42), HOP-62 (6.07, 4.85, 4.39), HOP-92 (6.03, 4.89, 4.38), NCI−H226 (5.66, 4.85, 4.11), NCI−H23 (5.49, 4.72, 4.29), NCI−H322M (5.47, 4.77, 4.37), NCI−H460 (6.57, 4.89, 4.24), NCI−H522 (5.52, 4.77, 4.40) [III] COLO205 (6.21, 5.62, 5.17), HCC-2998 (5.44, 4.96, 4.46), HCT-116 (6.24, 5.18, 4.64), HCT-15 (5.72, 5.16, 4.47), HT29 (6.43, 5.68, 5.26), KM12 (5.89, 5.03, 4.74), SW-620 (6.17, 5.51, 4.77) [IV] SF-268 (5.36, 4.62, 4.12), SF-295 (7.62, 6.54, 5.41), SF-539 (6.82, 5.70, 4.85), SNB-19 (6.40, 4.80, 4.39), SNB-75 (7.60, 5.74, 4.22), U251 (6.70, 4.62, 4.31) [V] LOX IMVI (6.42, 4.77, 4.51), MALME−3M (5.06, 4.57, 4.16), M14 (6.85, 5.92, 5.38), SK-MEL-2 (5.74, 4.77, 4.33), SK-MEL-28 (5.96, 4.89, 4.28), SK-MEL-5 (6.68, 5.05, 4.54), UACC-257 (5.24, 4.68, 4.33), UACC-62 (6.48, 5.64, 5.00) [VI] IGROV1 (5.62, 4.74, 4.37), OVCAR-3 (5.41, 4.89, 4.37), OVCAR-4 (4.92, 4.30, 4.11), OVCAR-5 (5.15, 4.72, 4.35), OVCAR-8 (4.96, 4.57, 4.19), SK−OV-3 (5.59, 4.80, 4.39) [VII] 786−0 (7.66, 5.72, 4.85), A498 (5.77, 4.77, 4.35), ACHN (5.37, 4.70, 4.36), CAKI-1 (5.72, 4.54, 4.12), RXF-393 (8.00, 6.57, 5.15), SN12C (4.92, 4.54, 4.17), TK-10 (5.21, 4.66, 4.28), UO-31 (7.12, 6.04, 5.28) [VIII] PC-3 (6.60, 4.89, 4.37), DU-145 (5.47, 4.72, 4.30) [IX] MCF7 (6.70, 5.22, 4.41), MCF7/ADR−RES (5.16, 4.52, 4.12), MDA-MB-231 (5.19, 4.42, 4.09), HS 578T (7.70, 5.96, 4.00), MDA-MB-435 (5.12, 4.48, 4.14), MDA-N (5.47, 4.82, 4.54), BT-549 (4.96, 4.40, 4.08), T-47D (4.96, 4.16, 4.00).

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