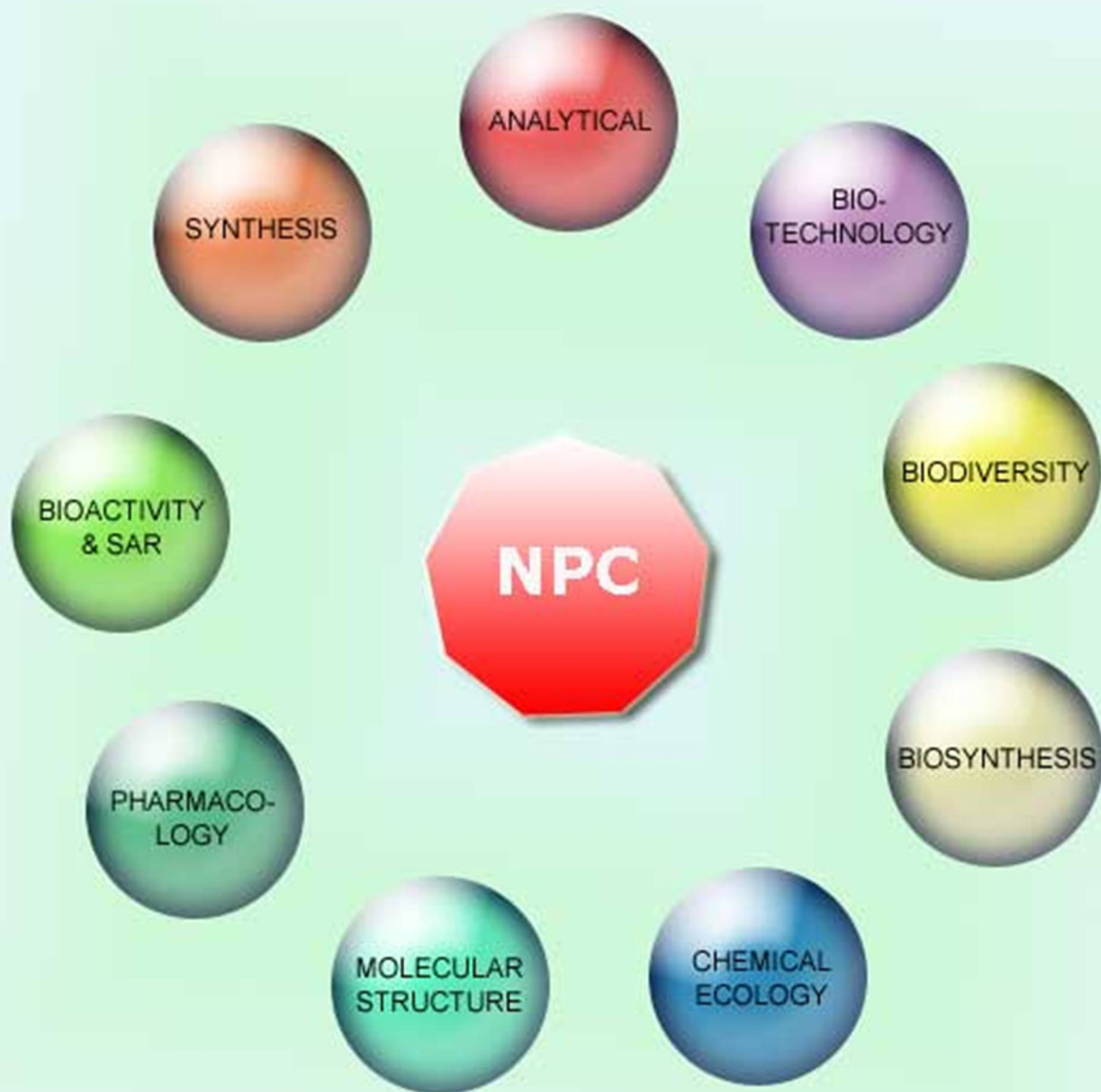


NATURAL PRODUCT COMMUNICATIONS

An International Journal for Communications and Reviews Covering all
Aspects of Natural Products Research



Volume 7. Issue 10. Pages 1259-1406. 2012
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
www.naturalproduct.us

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Cytotoxic Bioactivity of some Phenylpropanoic Acid Derivatives

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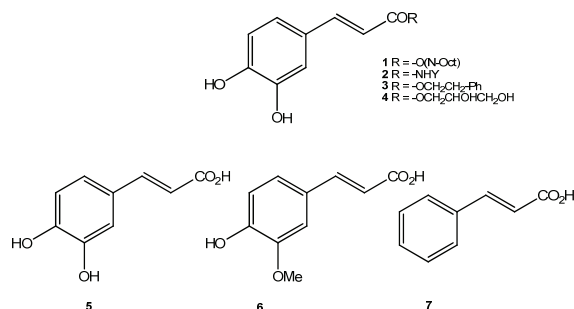
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Received: January 23rd, 2012; Accepted: August 27th, 2012

In this study, we synthesized a series of phenylpropanoic acid derivatives based on modifications at four selected points of the molecular scaffold. The *in vitro* antiproliferative activities of the compounds were examined in representative human solid tumor cell lines. A SAR was established pointing out the relevance of the substituents. The best activity profiles were obtained for the derivatives bearing more lipophilic esters (GI₅₀ 3.1-21 μM).

Keywords: Phenylpropanoic acids, Antitumor, Structure-activity relationship.

Phenylpropanoic acids such as caffeic, ferulic, and cinnamic acids, together with their analogues (**1-7**) are widely distributed in nature. Previous studies have shown that some caffeic acid derivatives possess a wide range of biological activities, including anticancer **0**, antibacterial **0**, antioxidant **0**, and antiviral **0**. Caffeic acid phenyl ethyl ester (CAPE, **3**), first isolated from beeswax in 1988, was proved to have remarkable cytotoxicity in tumor and virally transformed cells, but not in normal cells **0**. Furthermore, **3** is a constituent of natural honey-propolis and demonstrated strong antitumor effects in oral cancer cells. Despite the reports on anticancer activities of **3** and its derivatives, little is known about their mechanism of action.



For years, cancer researchers have been trying to find a way to target chemotherapeutic agents more precisely, to deliver the agents not only to that part of the body affected by a cancer, but to the internal areas of the tumor. In this context, an important point of attention is the development of new approaches to facilitate the uptake of chemotherapeutic agents into cancer cells. The cell membrane that surrounds each cell is a highly lipophilic structure and represents the ultimate drug penetration barrier. Among the proposed methods to enhance the passive internalization of drugs into cells, increasing their lipophilicity has often been demonstrated as a successful way. Some cytotoxic agents have been improved via these so-called prodrug approaches **0**. The traditional approach to increase drug lipophilicity consists in the introduction of long aliphatic chains, generally in the form of fatty acid esters or phosphate esters **0**. Lipophilicity of antitumor drugs also can be

increased by the addition of low molecular weight fragments, either at the main backbone or blocking polar functional groups. In this particular context, we reported earlier the enhancement of cytotoxicity in *tert*-butyldimethylsilyl (TBS) containing compounds with respect to their parent derivatives **0**.

In this work we report the antiproliferative activities of a small set of more lipophilic caffeic (**5**), ferulic (**6**) and cinnamic (**7**) acid derivatives. In order to perform structure-activity relationship (SAR) studies, we envisioned four possible points of modification of the molecular scaffold (Table 1): the ester residue (Z), the α,β -unsaturated carbonyl group (X), and the *para* (R) and *meta* (R') substituents on the aromatic ring.

The preparation of caffeic acid derivatives was carried out as shown in Figure 1. Ester derivatives were obtained by means of conventional esterification methods reported in the literature and were chosen in order to optimize yields (see Experimental). Briefly, ester **8** was obtained by reacting **5** with CH₂N₂ in diethyl ether; ester **11** was prepared by activation with dicyclohexylcarbodiimide (DCC); esters **14** and **15** were prepared by Fischer esterification using the corresponding alcohol; ester **13** was obtained by activation with chlorotrimethylsilane in ethanol **0**; and finally, ester **17** was prepared by treatment with methyl sulfate in acetone **0**. Acetylated derivatives in the aromatic ring **9**, **12** and **16** were prepared under typical acetylation conditions from alcohols **8**, **11** and **5**, respectively **0**. Saturated derivatives **10** and **19** were obtained by hydrogenation using Pd on charcoal as catalyst and EtOAc as solvent. Finally, saponification of **17** under alkaline conditions led to **18**.

The preparation of ferulic and cinnamic acid derivatives was carried out as shown in Figure 2. Compounds **20** and **22** were obtained by catalytic hydrogenation of ferulic (**6**) and cinnamic (**7**) acids, respectively. Esters **21**, **23**, and **24** were prepared by treating **6**, **7**, and **22** with CH₂N₂ in diethyl ether, respectively.

Lipophilicity is an important physico-chemical property to take into account in the design and development of any given drug. According to Lipinski, lipophilicity is one of the four parameters

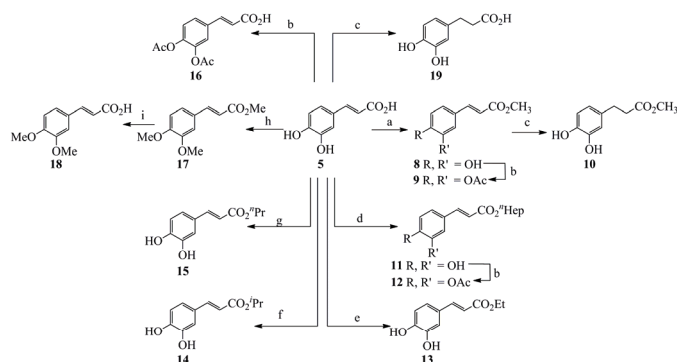


Figure 1: Reagents and conditions: a) CH_2N_2 , Et_2O , 81%; b) Ac_2O , DMAP, Py, 85% for **9**, 76% for **12**, 78% for **16**; c) H_2 , Pd/C, 1 atm, AcOEt, 75% for **10**, 88% for **19**; d) DCC, DMAP, *n*-heptanol, 66%; e) $(\text{CH}_3)_3\text{SiCl}$, EtOH, 93%; f) HCl, *i*-PrOH, 60%; g) HCl, *n*-PrOH, 72%; h) Me_2SO_4 , K_2CO_3 , NaF, acetone, 78%; i) KOH, H_2O , 54%.

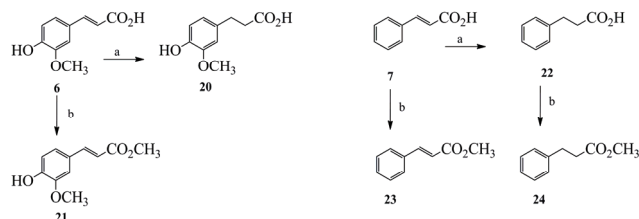


Figure 2: Reagents and conditions: a) H_2 , Pd/C, 1 atm, AcOEt, 83% for **20**, 95% for **22**; b) CH_2N_2 , Et_2O , 84% for **21**, 79% for **23**, 85% for **24**.

that should be globally associated with drug solubility and drug permeability through cell membranes. The octanol/water partition coefficient (K_{ow}) is widely used to express the lipophilicity of drugs. K_{ow} corresponds to the ratio of a compound's concentration in octanol to its concentration in water when both phases reach the equilibrium. Because the values of K_{ow} can range over many orders of magnitude, it is commonly expressed in logarithmic form ($\log K_{ow}$ or $\log P$). Partition coefficients can be determined either experimentally or calculated. The latter are called $\text{Clog}P$ (calculated $\log P$) or $\text{Mlog}P$ (Moriguchi $\log P$) if the Hansch-Leo's fragment constant method 0 or Moriguchi's method 0 are used, respectively. However, $\text{Clog}P$ values are more accurate than $\text{Mlog}P$ values. There exist several computer programs that calculate the $\text{Clog}P$ values 0, with $\text{Clog}P^{\text{R}}$ the more accurate predictor and the one chosen for our study 0.

The $\text{Clog}P$ values for compounds **5-24** were in the range 0.64 to 4.38 and are given in Table 1. $\text{Clog}P$ values were calculated to correlate lipophilicity with the biological activity. Overall, a direct correlation between lipophilicity of the side chain (Z) and antiproliferative activity was obtained.

The *in vitro* antiproliferative activity of compounds **5-24** was evaluated using the National Cancer Institute (NCI) protocol 0 after 48 h of drug exposure using the sulforhodamine B (SRB) assay 0. The results expressed as 50% growth inhibition (GI_{50}) are shown in Table 1. From the GI_{50} values, some structure-activity relationships can be inferred, as follows. When comparing the three parental drugs **5-7**, caffeic acid (**5**) was the only compound to inhibit cell growth in the most sensitive cell lines HBL-100 and SW1573, with GI_{50} values of 49 and 35 μM , respectively. This trend was observed for the three families. Thus, caffeic acid derivatives were more active than the corresponding ferulic and cinnamic series. With the exception of caffeic acid (**5**), all derivatives bearing carboxylic acids were inactive ($\text{GI}_{50} > 100 \mu\text{M}$) against all cell lines. The most active compounds of the series were analogs **11** and **12**, which showed GI_{50} values in the range 3.1-21 μM .

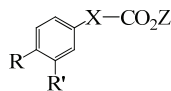
From the aforementioned four intervention points in the molecular scaffold, the most relevant for activity was the side chain ester (Z). In this particular feature, a direct relationship between lipophilicity and activity was obtained. This observation is more evident for the more resistant cell lines T-47D and WiDr. The order of activity was established *n*-Hep > *n*-Pr \approx *i*-Pr \approx Et > Me. The α,β -unsaturated group, although not essential in the case of HBL-100, HeLa and SW1573 cells, contributes positively to the biological activity (**8** > **10**), as shown with T-47D and WiDr cells. The replacement of the aromatic hydroxyl groups for methoxy groups produces a decrease in activity or even inactivation of the compound (**5** > **6**, **8** > **21** > **17**). From the data, it appears that a *m*-OH group is more relevant for activity than the *p*-OH (**8** > **21** > **17**). However, the acetylation of the hydroxyl groups does not produce a significant change in activity (**8** \approx **9**, **11** \approx **12**, **5** \approx **16**).

In summary, we have synthesized a small subset of phenylpropionic acid derivatives paying attention to four structural moieties in the general scaffold. The analysis of the antiproliferative activity in human solid tumor cell lines gave a SAR, pointing out some tips for further development of new analogs. Although preliminary, the

Table 1: Lipophilicity and *in vitro* antiproliferative activity against representative human solid tumor cell lines.^a

Compounds	$\text{Clog}P^b$	R	R'	X	Z	Cell line				
						HBL-100	HeLa	SW1573	T47D	WiDr
5	0.98	OH	OH	CH=CH	H	49 (± 7.3)	na	35 (± 0.9)	na	na
6	1.42	OH	OMe	CH=CH	H	na	na	na	na	na
7	2.24	H	H	CH=CH	H	na	na	na	na	na
8	1.20	OH	OH	CH=CH	Me	8.6 (± 4.4)	42 (± 18)	15 (± 5.1)	64 (± 0.4)	89 (± 9.7)
9	0.98	OAc	OAc	CH=CH	Me	17 (± 9.3)	39 (± 18)	9.8 (± 0.2)	87 (± 18)	87 (± 21)
10	1.05	OH	OH	CH ₂ -CH ₂	Me	10 (± 3.7)	46 (± 12)	21 (± 5.6)	na	na
11	4.38	OH	OH	CH=CH	<i>n</i> -Hep	5.2 (± 1.0)	4.1 (± 0.8)	2.9 (± 1.4)	16 (± 4.0)	16 (± 1.1)
12	4.16	OAc	OAc	CH=CH	<i>n</i> -Hep	3.1 (± 0.7)	4.0 (± 1.0)	3.4 (± 0.6)	21 (± 1.1)	21 (± 1.2)
13	1.73	OH	OH	CH=CH	Et	8.1 (± 1.9)	28 (± 3.9)	12 (± 2.6)	54 (± 16)	30 (± 7.6)
14	2.04	OH	OH	CH=CH	<i>i</i> -Pr	16 (± 3.3)	14 (± 6.4)	13 (± 2.9)	42 (± 4.0)	28 (± 7.2)
15	2.26	OH	OH	CH=CH	<i>n</i> -Pr	6.6 (± 0.4)	22 (± 4.3)	18 (± 5.9)	40 (± 5.2)	31 (± 8.5)
16	0.76	OAc	OAc	CH=CH	H	na	na	na	na	na
17	2.12	OMe	OMe	CH=CH	Me	na	na	na	na	na
18	1.90	OMe	OMe	CH=CH	H	na	na	na	na	na
19	0.64	OH	OH	CH ₂ -CH ₂	H	na	na	na	na	na
20	1.09	OH	OMe	CH ₂ -CH ₂	H	na	na	na	na	na
21	1.65	OH	OMe	CH=CH	Me	na	42 (± 3.7)	na	na	na
22	1.90	H	H	CH ₂ -CH ₂	H	na	na	na	na	na
23	2.47	H	H	CH=CH	Me	na	na	na	na	na
24	2.28	H	H	CH ₂ -CH ₂	Me	na	na	na	na	na

^a Values, expressed as GI_{50} (50% growth inhibition), are given in μM and are means of two to four experiments; standard deviation is given in parentheses. ^b Ref. 0.



results indicate the relevance of the synthetic derivatives of caffeic acid in the search for new antitumor drugs. Additionally, the results show specificity of the compounds when comparing the antiproliferative screening with the antimicrobial assays.

Experimental

General procedure: Caffeic acid (**5**), ferulic acid (**6**), cinnamic acid (**7**), dimethylaminopyridine (DMAP), potassium carboxide and methyl iodide were purchased from the Aldrich Chemical Company. 1,3-Dicyclohexylcarbodiimide (DCC) and sodium sulfate hydrate were purchased from the Sigma-Aldrich Chemical Company. Synthesized products were purified on a silica gel column and identified by TLC, NMR, IR and GC/Mass analysis. NMR spectra were recorded on a Bruker-Advance 200 spectrometer. Mass spectra (MS) were recorded on a Finnigan-Mat-GCQ-plus mass spectrometer. TLC was performed on precoated silical gel F254 plates (Merck) using a 254 nm UV lamp to monitor these reactions.

(E)-Methyl 3-(3,4-dihydroxyphenyl)acrylate (8): To a stirred solution of caffeic acid (**5**) (100 mg, 0.56 mmol) in anhydrous diethyl ether (50 mL) at 0°C was added, dropwise, a solution of diazomethane in diethyl ether. The reaction was monitored by TLC. After completion, the reaction mixture was removed from the ice bath and left 30 min at room temperature. After this time, the solvent was removed under reduced pressure. The resulting residue was purified by silica gel CC using *n*-hexane: EtOAc (7:3) as eluent to afford 87.07 mg of **8** as yellow oil. Yield: 81%.

¹H NMR (200 MHz, CD₃OD): 3.80 (3H, s, -OCH₃), 6.38 (1H, d, *J* = 16 Hz, H-8), 7.22 (1H, d, *J* = 8 Hz, H-5), 7.37 (1H, dd, *J* = 2 and 8 Hz, H-3), 7.43 (1H, d, *J* = 2 Hz, H-1), 7.63 (1H, d, *J* = 16 Hz, H-7). ¹³C NMR (50.23 MHz, CD₃OD) in full agreement with the literature.

Anal. Calcd for C₁₀H₁₀O₄: C, 61.85; H, 5.19; O, 32.96. Found C, 61.83; H, 5.23; O, 32.94.

Preparation of (E)-4-(3-methoxy-3-oxoprop-1-enyl)-1,2-phenylene diacetate (9): To a stirred solution of **8** (100 mg, 0.52 mmol) in dry pyridine (1.03 mL) at room temperature were sequentially added acetic anhydride (131.4 mg, 1.3 mmol) and 4-dimethylaminopyridine (6.3 mg, 0.05 mmol). The reaction mixture was left with stirring overnight, protected from light, and monitored by TLC. When the reaction was completed, 20 mL of ice-cold distilled water and 20 mL of diethyl ether were added. The organic phase was washed with 5% copper sulfate (3 x 20 mL) and water (2 x 20 mL). The organic fraction was dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The resulting residue was purified by CC on silica gel using *n*-hexane: EtOAc (7:3) as eluent. We obtained 122 mg of **9** as yellow oil. Yield: 85%.

¹H NMR (200 MHz, CD₃OD): 2.30 (3H, s, CH₃), 2.31 (3H, s, CH₃), 3.80 (3H, s, -OCH₃), 6.38 (1H, d, *J* = 16 Hz, H-8), 7.22 (1H, d, *J* = 8 Hz, H-5), 7.37 (1H, dd, *J* = 2 and 8 Hz, H-3), 7.43 (d, *J* = 2 Hz, H-1), 7.63 (1H, d, *J* = 16 Hz, H-7). These spectral data were in agreement with the diacetyl derivative of compound **8**.

Anal. Calcd for C₁₄H₁₄O₆: C, 60.43; H, 5.07; O, 34.50. Found C, 60.41; H, 5.10; O, 34.49.

Preparation of methyl 3-(3,4-dihydroxyphenyl)propanoate (10): Pd/C (22 mg) was added in one portion to a solution of **9** (200 mg, 1.03 mmol) in EtOAc (50 mL). The mixture was stirred under a hydrogen atmosphere for 2 h. Then, the catalyst was removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel, using *n*-hexane: EtOAc (7:3). 158 mg of **10** was obtained as yellow oil. Yield: 75%.

¹H NMR (400 MHz, CDCl₃): 2.62 (2H, t, *J* = 7 Hz, H-8), 2.85 (2H, t, *J* = 7 Hz, H-7), 3.70 (3H, s, -OCH₃), 6.62 (1H, dd, *J* = 2, 8 Hz, H-2), 6.72 (1H, d, *J* = 2 Hz, H-6), 6.78 (1H, d, *J* = 8 Hz, H-5).

¹³C NMR (100.5 MHz, CDCl₃): 30.25 (CH₂), 35.95 (CH₂), 51.87 (CH₃), 115.38 (2 CH), 120.48 (CH), 133.17 (C), 142.14 (C), 143.67 (C), 174.28 (C).

Anal. Calcd for C₁₀H₁₂O₄: C, 61.22; H, 6.16; O, 32.62. Found C, 61.19; H, 6.20; O, 32.61.

Preparation of (E)-heptyl 3-(3,4-dihydroxyphenyl)acrylate (11):

To a stirred solution of **5** (200 mg, 1.12 mmol) in dichloromethane (30 mL) were added dicyclohexylcarbodiimide (347 mg, 1.68 mmol) and 4-dimethylaminopyridine (205 mg, 1.68 mmol). The mixture was stirred for 30 min and then 1-heptanol (156.6 mg, 190.5 μL, 1.34 mmol) was added. The reaction mixture was filtered through celite to remove the dicyclohexylurea generated. The organic layer was washed twice with 10% HCl to remove the base and then once with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using 60G Sigel and *n*-hexane: EtOAc (7:3) as eluent; 203.9 mg of **11** was recovered as yellow oil. Yield: 66%.

¹H NMR (400 MHz, CD₃OD): 0.93 (3H t, *J* = 6 Hz, CH₃, "Hep side chain), 1.39-1.30 (8H m 4 CH₂ "Hep side chain), 1.70 (2H, m, CH₂ "Hep side chain), 4.17 (2H, t, *J* = 6.8 Hz, -OCH₂- *n*-hep side chain), 6.27 (d, *J* = 16 Hz, 1H, H-8), 6.80 (d, *J* = 8.4 Hz, 1H, H-5), 6.90 (1H, d, *J* = 8.4 Hz, H-2), 7.06 (1H, s, H-6), 7.55 (1H, d, *J* = 16 Hz, H-7).

¹³C NMR (100.5 MHz, CD₃OD): 13.01 (CH₃, "Hep side chain); 22.25 (CH₂, "Hep side chain); 25.66 (CH₂, "Hep side chain); 28.47 (CH₂, "Hep side chain); 28.68 (CH₂, "Hep side chain); 31.51 (CH₂, "Hep side chain); 64.18 (CH₂, "Hep side chain); 113.70 (CH); 113.81 (CH); 115.08 (CH); 121.50 (CH); 126.31 (C); 145.35 (CH); 145.51 (C*); 148.13 (C*); 167.99 (C); (*: interchangeable).

Anal. Calcd for C₁₆H₂₂O₄: C, 69.04; H, 7.97; O, 22.99. Found C, 69.02; H, 7.99; O, 22.97.

Preparation of (E)-4-(3-(heptyloxy)-3-oxoprop-1-enyl)-1,2-phenylene diacetate (12):

To a stirred solution of **11** (150 mg, 0.54 mmol) in dry pyridine (1.08 mL) was added acetic anhydride (137.5 mg, 1.35 mmol) and 4-dimethylaminopyridine (6.59 mg, 0.05 mmol). The reaction mixture was left with stirring overnight, protected from light, and monitored by TLC. When the reaction was complete, 20 mL of cold distilled water and 20 mL of diethyl ether were added. The organic phase was washed with 5% copper sulfate (3 x 20 mL) and water (2 x 20 mL). The organic fraction was dried with anhydrous Na₂SO₄, and the solvent removed under reduced pressure. The resulting residue was purified by CC on silica gel using *n*-hexane: EtOAc (7:3) as eluent; 147.4 mg of **12** was obtained as white powder. Yield: 76%.

¹H NMR (200 MHz, CDCl₃): 0.92 (3H, t, *J* = 6.2 Hz, -OCH₃, "Hep side chain); 1.25-1.34 (8H, m, CH₂, "Hep side chain); 1.68 (2H, m, CH₂, "Hep side chain); 2.30 (6H, s, -OCOCH₃); 4.19 (2H, t, *J* = 6.3 Hz, CH₂, "Hep side chain); 6.38 (1H, d, *J* = 16 Hz, H-8); 7.21 (1H, d, *J* = 8.2 Hz, H-5); 7.37 (1H, dd, *J* = 8.2 and 2 Hz, H-2); 7.42 (1H, d, *J* = 2 Hz, H-6); 7.61 (1H, d, *J* = 16 Hz, H-7).

¹³C NMR (50.23 MHz, CDCl₃): 13.8 (CH₃, "Hep side chain); 22.4*, 25.6*, 28.6*, 31.4* (CH₂, "Hep side chain); 28.5 (CH₂, "Hep side chain); 20.4 (OCOCH₃); 64.6 (-OCH₂, "Hep side chain); 119.2 (CH); 122.4 (CH); 123.7 (CH); 126.2 (CH); 133.3 (C); 142.6 (CH); 143.0 (CH); 166.5 (C); 167.9 (-OCOCH₃).

Anal. Calcd for C₂₀H₂₆O₆: C, 66.28; H, 7.23; O, 26.49. Found C, 66.24; H, 7.25; O, 26.51.

Preparation of (E)-ethyl 3-(3,4-dihydroxyphenyl)-acrylate (13): To a stirred solution of **5** (100 mg, 0.56 mmol) in dry ethanol (5 mL) at room temperature was added, dropwise, trimethylchlorosilane (0.11 mL, 0.79 mmol). The reaction mixture was stirred overnight. After completion, as monitored by TLC, the solvent was removed under reduced pressure. The resulting residue was purified by CC on silica gel using *n*-hexane: EtOAc (7:3) as eluent to give 107.96 mg of **13** as yellow oil. Yield: 93%.

¹H NMR (400 MHz, CD₃OD): 1.32 (3H, t, *J* = 7.2 Hz, CH₃, side chain), 4.23 (2H, c, *J* = 7.2 Hz, CH₂, side chain), 6.26 (1H, d, *J* = 16 Hz, H-8), 6.79 (1H, d, *J* = 8 Hz, H-5), 6.95 (1H, dd, *J* = 2 and 8 Hz, H-2), 7.05 (1H, d, *J* = 2 Hz, H-6), 7.54 (1H, d, *J* = 16 Hz, H-7). ¹³C NMR (100.5 MHz, CD₃OD): 13.23 (CH₃, side chain); 60.02 (-OCH₂, side chain); 113.69 (CH); 113.85 (CH); 115.09 (CH); 121.49 (CH); 126.32 (C); 145.32 (CH); 145.39 (C); 148.12 (C); 167.93 (C). Anal. Calcd for C₁₁H₁₂O₄: C, 63.45; H, 5.81; O, 30.74. Found C, 63.41; H, 5.87; O, 30.72.

Preparation of (E)-isopropyl 3-(3,4-dihydroxyphenyl)-acrylate (14): To a stirred solution of **5** (200 mg, 1.12 mmol) in isopropyl alcohol (30 mL) was added concentrated HCl (0.5 mL, 37%, v/v). The reaction mixture was stirred for 3 h at reflux temperature. The excess alcohol was removed under reduced pressure, and the residue taken up with water and extracted with diethyl ether (3 x 15 mL). The organic layer was washed with bicarbonate solution (pH = 9.7), followed by distilled water, and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and purified by CC on silica gel using *n*-hexane: EtOAc (7:3) as solvent to afford 147.74 mg of **14**. Yield: 60%.

¹H NMR (400 MHz, CD₃OD): 1.30 (6H, d, *J* = 6.4 Hz, CH₃, side chain); 5.08 (1H, m, -OCH, side chain); 6.24 (1H, d, *J* = 16 Hz, H-8); 6.79 (1H, d, *J* = 8 Hz, H-5); 6.95 (1H, dd, *J* = 2 and 8 Hz, H-2); 7.05 (1H, d, *J* = 2 Hz, H-6); 7.53 (1H, d, *J* = 16 Hz, H-7). ¹³C NMR (100.5 MHz, CD₃OD): 20.77 (CH₃, side chain); 67.52 (OCH, side chain); 113.67 (CH); 114.34 (CH); 115.09 (CH); 121.45 (CH); 126.35 (C); 145.11 (CH); 145.39 (C); 148.08 (C). Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35; O, 28.80. Found C, 64.82; H, 6.39; O, 28.79.

Preparation of (E)-propyl 3-(3,4-dihydroxyphenyl)-acrylate (15): To a stirred solution of **5** (200 mg, 1.12 mmol) in *n*-propyl alcohol (50 mL) was added concentrated HCl (0.5 mL, 37%, v/v). The reaction mixture was stirred for 3 h at reflux temperature. The excess alcohol was removed under reduced pressure, and the residue taken up with water and extracted with diethyl ether (3 x 15 mL). The organic layer was washed with bicarbonate solution (pH = 9.7), followed by distilled water, and dried with anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and purified by CC on silica gel using *n*-hexane: EtOAc (7:3) as solvent to afford 176.45 mg of **15** as yellow oil. Yield: 72%.

¹H NMR (400 MHz, CD₃OD): 1.01 (3H, t, *J* = 7.2 Hz, CH₃, side chain), 1.73 (2H, m, CH₂, side chain), 4.14 (2H, t, *J* = 6.4 Hz, -OCH₂, side chain), 6.27 (1H, d, *J* = 16 Hz, H-8), 6.79 (1H, d, *J* = 8 Hz, H-5), 6.96 (1H, dd, *J* = 2 and 8 Hz, H-2), 7.05 (1H, d, *J* = 2 Hz, H-6), 7.55 (1H, d, *J* = 16 Hz, H-7). ¹³C NMR (100.5 MHz, CD₃OD): 9.34 (CH₃, side chain); 21.77 (CH₂, side chain); 65.66 (OCH₂, side chain); 113.69 (CH); 113.79 (CH); 115.09 (CH); 121.49 (CH); 126.32 (C); 145.35 (CH); 145.39 (C); 148.13 (C); 168.01 (C). Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35; O, 28.80. Found C, 64.82; H, 6.40; O, 28.78.

Preparation of (E)-3-(3,4-diacetoxyphenyl)acrylic acid (16): To a stirred solution of **5** (100 mg, 0.56 mmol) in dry pyridine (1.2 mL) were added acetic anhydride (2.7 mL, 1.4 mmol) and 4-dimethyl-

aminopyridine (6.8 mg, 0.056 mmol). The reaction mixture was left with stirring overnight, protected from light, and monitored by TLC. When the reaction was complete, 20 mL of cold distilled water and 20 mL of diethyl ether were added. The organic phase was washed with copper sulfate 5% (3 x 20 mL) and water (2 x 20 mL). The organic fraction was dried with anhydrous sulfate, filtered, and the solvent removed under reduced pressure. The resulting residue was purified by CC on silica gel using *n*-hexane: EtOAc (7:3) as eluent; 115 mg of **16** was obtained as yellow oil. Yield: 78%.

¹H NMR: In full agreement with the literature 0.

Anal. Calcd for C₁₃H₁₂O₆: C, 59.09; H, 4.58; O, 36.33. Found C, 59.05; H, 4.60; O, 36.35.

Preparation of (E)-methyl 3-(3,4-dimethoxyphenyl)-acrylate (17): A stirred solution of **5** (200 mg, 1.12 mmol), K₂CO₃ (1.6 g, 11.7 mmol), and NaF (0.49 g, 11.7 mmol) in acetone (10 mL) was heated until reflux. Then, methyl sulfate (1.26 g, 9.9 mmol) was added dropwise. After 2 h the reaction was complete (controlled by TLC). The reaction mixture was cooled and filtered through celite. The organic phase was washed with a saturated solution of NaHCO₃, and then dried with anhydrous Na₂SO₄, filtered and concentrated; 192 mg of **17** was obtained as yellow oil. Yield: 78%.

¹H NMR (200 MHz, CDCl₃ and CD₃OD): 3.77 (3H, s, -COOCH₃), 3.88 (3H, s, -OCH₃), 3.89 (3H, s, -OCH₃), 6.31 (1H, d, *J* = 16 Hz, H-8), 6.86 (1H, d, *J* = 8 Hz, H-5), 7.09 (2H, m, H-2 and H-6), 7.61 (1H, d, *J* = 16 Hz, H-7).

¹³C NMR (50.25 MHz, CDCl₃ and CD₃OD): 51.0 (-COOCH₃); 55.3 (-O*CH₃); 55.4 (-O*CH₃); 109.3 ([#]CH); 110.7 (CH); 115.0 (CH); 122.2 ([#]CH); 126.8 (C); 144.3 (CH); 148.8 (C); 150.8 (C); 167.1 (C). The values of * and [#] are interchangeable.

Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35; O, 28.80. Found C, 64.87; H, 6.34; O, 28.79.

Preparation of (E)-3-(3,4-dimethoxyphenyl)acrylic acid (18): To a stirred solution of **17** (100 mg, 0.45 mmol) in EtOAc (5 mL) was added a solution of KOH (25.2 mg, 0.45 mmol) in distilled water (30 mL). The mixture was refluxed until completion, as monitored by TLC. The solution was acidified with HCl (5% in water). The mixture was extracted with diethyl ether (3 x 20 mL), dried with Na₂SO₄, filtered, and concentrated on a rotary evaporator. The residue was purified by silica gel CC using *n*-hexane: EtOAc (7:3) to obtain 50.6 mg of **18** as yellow oil. Yield: 54%.

¹H NMR (400 MHz, CDCl₃): 3.92 (6H, s, -OCH₃), 6.32 (1H, d, *J* = 16 Hz, H-8), 6.88 (1H, d, *J* = 8.4 Hz, H-5), 7.13 (2H, m, H-2 and H-6), 7.73 (1H, d, *J* = 16 Hz, H-7).

¹³C NMR (100.5 MHz, CDCl₃): 55.9 (-OCH₃*), 56.0 (-OCH₃*), 109.7 ([#]CH), 110.9 (CH), 114.8 (CH), 123.1 ([#]CH), 127.0 (C), 147.0 (CH), 149.2 (C), 151.5 (C), 172.5 (C). The values of * and [#] are interchangeable.

Anal. Calcd for C₁₁H₁₂O₄: C, 63.45; H, 5.81; O, 30.74. Found C, 63.42; H, 5.86; O, 30.72.

Preparation of 3-(3,4-dihydroxyphenyl)propanoic acid (19): Pd/C (22 mg) was added in one portion to a solution of **5** (200 mg, 1.12 mmol) in EtOAc (50 mL). The mixture was stirred under hydrogen for 2 h and the catalyst removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel using *n*-hexane: EtOAc (7:3) to give 177.35 mg of **19**. Yield: 88%.

¹H NMR (400 MHz, CDCl₃): 2.72 (2H, t, *J* = 8 Hz, H-8), 3.00 (2H, t, *J* = 8 Hz, H-7); 7.33-7.24 (5H, m).

¹³C NMR (100.5 MHz, CDCl₃): 30.5 (CH₂), 35.6 (CH₂), 126.4 (CH), 128.3 (CH), 128.6 (CH), 133.3 (C), 144.1 (C), 146.8 (C), 179.1 (C).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53; O, 35.13. Found C, 59.30; H, 5.58; O, 35.12.

Preparation of 3-(4-hydroxy-3-methoxyphenyl)-propanoic acid (20): Pd/C (20 mg) was added in one portion to a solution of **6** (100 mg, 0.52 mmol) in EtOAc (50 mL). The mixture was stirred under hydrogen for 2 h and the catalyst removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel using *n*-hexane: EtOAc (7:3) to give 83.86 mg of **20** as yellow oil. Yield: 83%.

1H NMR (400 MHz, $CDCl_3$): 2.68 (2H, t, $J = 7.6$ Hz, H-8), 2.92 (2H, t, $J = 7.6$ Hz, H-7), 3.89 (3H, s, -OCH₃), 6.73 (2H, m, H-2 and H-6), 6.86 (1H, d, $J = 8$ Hz, H-5).

^{13}C NMR (100.5 MHz, $CDCl_3$): 30.345 (CH₂), 35.95 (CH₂), 55.87 (-OCH₃), 110.92 (CH), 114.41 (CH), 120.84 (CH), 132.08 (C), 144.08 (C), 146.44 (C), 178.76 (C).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; O, 32.62. Found C, 61.18; H, 6.22; O, 32.60.

Preparation of (E)-methyl 3-(4-hydroxy-3-methoxyphenyl)acrylate (21): To a stirred solution of ferulic acid (**6**) (100 mg, 0.52 mmol) in anhydrous diethyl ether (50 mL) at 0°C was added, dropwise, a solution of diazomethane in diethyl ether. The reaction was monitored by TLC. After completion, the reaction mixture was removed from the ice bath and left for 30 min at room temperature. The solvent was then removed under reduced pressure. The resulting residue was purified by silica gel CC using *n*-hexane: EtOAc (7:3) to afford 93 mg of **21** as yellow oil. Yield: 84%.

1H NMR (400 MHz, CD_3OD): 3.80 (3H, s, -COOCH₃); 3.90 (3H, s, -OCH₃); 6.29 (1H, d, $J = 16$ Hz, H-8); 6.91 (1H, d, $J = 6.8$ Hz, H-5); 7.04 (1H, dd, $J = 6.8$ y 1.8 Hz, H-2); 7.10 (1H, d, $J = 1.8$ Hz, H-6); 7.62 (1H, d, $J = 16$ Hz, H-7).

^{13}C NMR (100.5 MHz, CD_3OD): 51.6 (-COOCH₃); 55.8 (-OCH₃); 109.2 (CH); 114.5 (CH); 115.0 (CH); 122.9 (CH); 126.9 (C); 144.9 (CH); 145.2 (C); 147.2 (C); 167.7 (C).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; O, 30.74. Found C, 63.43; H, 5.85; O, 30.72.

Preparation of 3-(4-hydroxy-3-methoxyphenyl)-propanoic acid (22): Pd/C (24 mg) was added in one portion to a solution of cinnamic acid (**7**) (100 mg, 0.68 mmol) in EtOAc (50 mL). The mixture was stirred under hydrogen for 2 h and the catalyst removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel, using a solution of *n*-hexane: EtOAc (7:3) to obtain 96.3 mg of **22** as yellow oil. Yield: 95%.

1H NMR (400 MHz, $CDCl_3$): 2.72 (2H, t, $J = 8$ Hz, H-8), 3.00 (2H, t, $J = 8$ Hz, H-7), 7.33-7.24 (5H, m, H₂-3-4-5-6).

^{13}C NMR ($CDCl_3$, 100.5 MHz): 30.58 (CH₂); 35.59 (CH₂); 126.38 (CH); 128.26 (d, CH* and CH*); 128.56 (d, C-2* and C-6*); 140.14 (C); 179.06 (C). The values of * are interchangeable.

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found C, 71.95; H, 6.73; O, 21.32.

Preparation of methyl 3-phenylpropanoate (23): To a stirred solution of **7** (100 mg, 0.68 mmol) in anhydrous diethyl ether (50 mL) at 0°C was added, dropwise, a solution of diazomethane in diethyl ether. The reaction was monitored by TLC. After completion, the reaction mixture was removed from the ice bath and left for 30 min at room temperature. After this time, the solvent was removed under reduced pressure. The resulting residue was purified by silica gel CC using *n*-hexane: EtOAc (7:3) as eluent to afford 83 mg of **23** as yellow oil. Yield: 79%.

1H NMR (400 MHz, $CDCl_3$): 3.83 (3H, s, -OCH₃), 6.47 (1H, d, $J = 16$ Hz, H-8), 7.40-7.55 (5H, m, H-2,3,4,5,6), 7.72 (1H, d, $J = 16$ Hz, H-7).

^{13}C NMR (100.5 MHz, $CDCl_3$): 51.69 (-OCH₃); 117.79 (CH); 128.06 (CH 2 y 6); 128.88 (CH and CH); 130.29 (CH); 134.38 (C); 144.86 (CH); 167.41 (C).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21; O, 19.73. Found C, 74.03; H, 6.25; O, 19.72.

Preparation of methyl cinnamate (24): To a stirred solution of **22** (100 mg, 0.66 mmol) in anhydrous diethyl ether (50 mL) at 0°C was added, dropwise, a solution of diazomethane in diethyl ether. The reaction was monitored by TLC. After completion, the reaction mixture was removed from the ice bath and left for 30 min at room temperature. After this time, the solvent was removed under reduced pressure. The resulting residue was purified by silica gel CC using *n*-hexane: EtOAc (7:3) as eluent to afford 88.5 mg of **24** as yellow oil. Yield: 85%.

1H NMR (400 MHz, $CDCl_3$): 2.62 (2H, t, $J = 8$ Hz, H-8), 2.95 (2H, t, $J = 8$ Hz, H-7), 3.65 (3H, s, -OCH₃); 7.17-7.28 (5H, m, H₂-H₆).

^{13}C NMR ($CDCl_3$, 100.5 MHz): 30.9 (CH₂); 35.7 (CH₂); 51.92 (-OCH₃); 126.3 (CH); 128.3 (CH* and CH*); 128.5 (CH* and CH*); 140.5 (C); 173.4 (C). The values of * are interchangeable.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.49. Found C, 73.10; H, 7.40; O, 19.50.

Biological studies: All starting materials were commercially available, research-grade chemicals, and were used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), fetal bovine serum (FBS) from Gibco (Grand Island, NY), trichloroacetic acid (TCA) and glutamine from Merck (Darmstadt, Germany), and Mueller Hinton broth from Becton Dickinson (San José, CA). Penicillin G, streptomycin, dimethylsulfoxide (DMSO), sulforhodamine B (SRB), and MOPS were from Sigma (St Louis, MO). Pure compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration, that is, 100 μ M.

Antiproliferative assay: The human solid tumor cell lines HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast) and WiDr (colon) were used in this study. These cell lines were a kind gift from Prof. Godefridus J. Peters (VU Medical Center, Amsterdam, The Netherlands) and Dr Rubén P. Machín (HUGC Dr Negrín, Las Palmas de Gran Canaria, Spain). Cells were maintained in 25 cm² culture flasks in RPMI 1640 supplemented with 5% FBS and 2 mM L-glutamine in a 37°C, 5% CO₂, 95% humidified air incubator. Exponentially growing cells were trypsinized and re-suspended in antibiotic containing medium (100 U penicillin G and 0.1 mg of streptomycin per mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated at 100 μ L per well at densities of 1×10^4 (HBL-100 and SW1573), 1.5×10^4 (HeLa and T-47D), and 2×10^4 (WiDr) cells per well, based on their doubling times. Each agent was tested in triplicate at different dilutions in the range of 1–100 μ M. The drug treatment was started on day 1 after plating. Drug incubation time was 48 h, after which time cells were precipitated with 25 μ L ice-cold TCA (50%, w/v) and fixed for 60 min at 4°C. Then the SRB assay was performed. The optical density (OD) of each well was measured at 492 nm, using BioTek's PowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium. The percentage of growth (PG) was calculated with respect to untreated control cells (C) at each of the drug concentration levels

based on the difference in OD at the start (T_0) and end of drug exposure (T), according to the National Cancer Institute (USA) formulas 0. Therefore, if T is greater than or equal to T_0 the calculation is $PG = 100 \times [(T-T_0)/(C-T_0)]$. If T is less than T_0 denoting cell killing the calculation is $PG = 100 \times [(T-T_0)/(T_0)]$. With these calculations, 3 levels of effect could be determined; 50% growth inhibition (GI_{50}), total growth inhibition (TGI), and 50% cell killing (LC_{50}) that represent the concentration at which PG is +50, 0, and -50, respectively. Thus, a PG value of 0 corresponds to the amount of cells present at the start of drug exposure, while negative PG values denote net cell kill.

Acknowledgments - This research was supported by CONICET (PIP 112-200801-00628), ANPCyT (PICT 2007-352), UNSL (Project 7301). Co-financed by the European Social Fund (FEDER): the Spanish MICIIN (CTQ2008-06806-C02-01/BQU), the Spanish MSC (RTICC RD06/0020/1046), the Canary Islands ACIISI (PI 2007/021), and FUNCIS (PI 35/06 and 43/09). L.G.L. and E.P.R. thank the Spanish MSC-FIS for postdoctoral contracts. J.M.P. thanks the Spanish MEC-FSE for a Ramón y Cajal contract.

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Thymofoloinates A and B, New Cinnamic Acid Derivatives from <i>Euphorbia thymifolia</i> Riaz Hussain, Bakhat Ali, Muhammad Imran and Abdul Malik	1351
Efficient Counter-current Chromatographic Isolation and Structural Identification of Two New Cinnamic Acids from <i>Echinacea purpurea</i> Ying Lu, JiaYin Li, MiLu Li, Xia Hu, Jun Tan and Zhong Hua Liu	1353
Norlignans from <i>Asparagus cochinchinensis</i> Xing-Nuo Li, Chu Chu, Dong-Ping Cheng, Sheng-Qiang Tong and Ji-Zhong Yan	1357
Novel Application of Mahua (<i>Madhuca</i> sp.) Flowers for Augmented Protease Production from <i>Aeromonas</i> sp. S1 Amrik Bhattacharya, Vandana Saini and Anshu Gupta	1359
Chemical Composition of the Fatty Oils of the Seeds of <i>Cleome viscosa</i> Accessions Rashmi Kumari, Gopal Rao Mallavarapu, Vinod Kumar Jain and Sushil Kumar	1363
Essential Oil and other Constituents from <i>Magnolia ovata</i> Fruit Leticia F. L. Barros, Carlos Augusto Ehrenfried, Dilamara Riva, Andersson Barison, Renato de Mello-Silva and Maria Elida A. Stefanello	1365
Chemical Composition of the Essential Oil of <i>Zingiber zerumbet</i> var. <i>darcyi</i> Virendra S. Rana, Mercedes Verdeguer and Maria A. Blazquez	1369
Compositions of the Volatile Oils of <i>Citrus macroptera</i> and <i>C. maxima</i> Virendra S. Rana and Maria A. Blazquez	1371
Chemical Compositions of Essential Oils from <i>Xylosteinum vietnamense</i> and <i>X. selinum leonidii</i> Tran Huy Thai, Nguyen Sinh Khang, Nguyen Thi Hien, Tran Minh Hoi and Nguyen Tien Dat	1373
Chemotaxonomical Markers in Essential Oil of <i>Murraya koenigii</i> Thilaghavani Nagappan, Perumal Ramasamy and Charles Santhanaraju Vairappan	1375
Essential Oil Composition and Antibacterial Activity of <i>Anthemis mixta</i> and <i>A. tomentosa</i> (Asteraceae) Carmen Formisano, Daniela Rigano, Felice Senatore, Francesco Maria Raimondo, Antonella Maggio and Maurizio Bruno	1379
Antifungal and Antibacterial Activity of the Essential oil of <i>Chamaecyparis lawsoniana</i> from Spain Jesús Palá-Paúl, Jaime Usano-Aleman, Elena Granda and Ana-Cristina Soria	1383
Chemical Composition and Biological Activities of Essential Oil from <i>Hyptis crenata</i> Growing in the Brazilian Cerrado Ivana Maria Póvoa Violante, Walmir Silva Garcez, Carolina da Silva Barbosa and Fernanda Rodrigues Garcez	1387
Larvicidal Activity against <i>Aedes aegypti</i> of Essential Oils from Northeast Brazil Patrícia L. Lavor, Gilvandete M. P. Santiago, Roberto W. da Silva Gois, Leôncio M. de Sousa, Gabrieli da P. Bezerra, Nirla R. Romero, Ângela M. C. Arriaga, Telma L. G. Lemos, Péricles B. Alves and Paulo C. S. Gomes	1391
Composition and Antipseudomonal Effect of Essential Oils Isolated from Different Lavender Species Anna Végh, Tímea Bencsik, Péter Molnár, Andrea Böszörményi, Éva Lemberkovics, Krisztina Kovács, Béla Kocsis and Györgyi Horváth	1393
Essential Oil of <i>Croton argyrophylloides</i>: Toxicological Aspects and Vasorelaxant Activity in Rats Aldair de França-Neto, Ana Carolina Cardoso-Teixeira, Thiago Coutinho Medeiros, Maria do Socorro Quinto-Farias, Celia Maria de Souza Sampaio, Andreлина Noronha Coelho-de-Souza, Saad Lahlou and José Henrique Leal-Cardoso	1397
Antimicrobial Activity of Blended Essential Oil Preparation Sarin Tadtong, Supatcha Suppawat, Anchalee Tintawee, Phanida Saramas, Suchada Jareonvong and Tapanee Hongratanaworakit	1401

Natural Product Communications

2012

Volume 7, Number 10

Contents

<u>Original Paper</u>	<u>Page</u>
HPLC Analysis and Cytotoxic Activity of <i>Vernonia cinerea</i> Mom Khay, Phiroom Toeng, Valérie Mahiou-Leddet, Fathi Mabrouki, Kim Sothea, Evelyne Ollivier, Riad Elias and Sok-Siya Bun	1259
Antiplasmodial Activity of the Ethnobotanical Plant <i>Cassia fistula</i> Mary H. Grace, Carmen Lategan, Rocky Graziöse, Peter J. Smith, Ilya Raskin and Mary Ann Lila	1263
Trichilone, a New C₂₁ Steroid from <i>Trichilia connaroides</i> Qiang Zhang, Yu Zhang, Hong-Ping He, Ying-Tong Di and Xiao-Jiang Hao	1267
Three Novel Immunosuppressive Steroidal Glycosides from the Stems of <i>Stephanotis mucronata</i> Xiao-yu Li, Shu-ling Zong, Feng-yang Chen, Shi-fang Xu and Yi-ping Ye	1269
Optimization of Carbon Source for Hairy Root Growth and Withaferin A and Withanone Production in <i>Withania somnifera</i> Ganeshan Sivanandhan, Manoharan Rajesh, Muthukrishnan Arun, Murugaraj Jeyaraj, Gnanajothi Kapil Dev, Markandan Manickavasagam, Natesan Selvaraj and Andy Ganapathi	1271
Quantitative Analysis of Substituted <i>N,N</i>-Dimethyl-tryptamines in the Presence of Natural Type XII Alkaloids Bojidarka Ivanova and Michael Spitteller	1273
HPLC Analysis of Stemokerrine and Oxystemokerrine in the Thai Medicinal Plant <i>Stemona kerrii</i> Sumet Kongkiatpaiboon, Vichien Keeratinijakal and Wandee Gritsanapan	1277
Identification of Pavinane Alkaloids in the Genera <i>Argemone</i> and <i>Eschscholzia</i> by GC-MS Lucie Cahlíková, Radim Kučera, Anna Hošťálková, Jiří Klimeš and Lubomír Opletal	1279
Effect of Piperine on the Pharmacokinetics and Pharmacodynamics of Glimpiride in Normal and Streptozotocin - induced Diabetic Rats Ciddi Veeresham, Samala Sujatha and Thatipamula Sandya Rani	1283
<i>In Silico</i> Prediction of the Cosmetic Whitening Effects of Naturally Occurring Lead Compounds Pedro Fong and Henry H. Y. Tong	1287
Profiling Flavonoid Cytotoxicity in Human Breast Cancer Cell Lines: Determination of Structure-Function Relationships Sina Yadegarynia, Anh Pham, Alex Ng, Duong Nguyen, Tetiana Lialiukska, Anthony Bortolazzo, Valentin Sivryuk, Martina Bremer and J. Brandon White	1295
Two New Flavonoids from the Seeds of <i>Derris scandens</i> Rachakunta Munikishore, Aluru Rammohan, Adivireddy Padmaja, Duvvuru Gunasekar, Alexandre Deville and Bernard Bodo	1305
Dihydroflavonol and Flavonol Derivatives from <i>Macaranga recurvata</i> Mulyadi Tanjung, Euis H. Hakim, Elfahmi, Jalifah Latip and Yana M. Syah	1309
Flavonoids Bearing an <i>O</i>-arabinofuranosyl-(1→3)-rhamnoside Moiety from <i>Cladocolea micrantha</i>: Inhibitory Effect on Human Melanoma Cells Anderson C. Guimaraes, Alvicler Magalhães, Marcos J. Nakamura, Antonio C. Siani, Christina Barja-Fidalgo and André L. F. Sampaio	1311
Effect of Seasonality on Chemical Composition and Antibacterial and Anticandida Activities of Argentine Propolis. Design of a Topical Formulation María Inés Isla, Yanina Dantur, Ana Salas, Carolina Danert, Catiana Zampini, Myriam Arias, Roxana Ordóñez, Luis Maldonado, Enrique Bedascarrasbure and María Inés Nieva Moreno	1315
Larvicidal Activity of Isoflavonoids from <i>Muelleria frutescens</i> Extracts against <i>Aedes aegypti</i> Charlotte Nirma, Alice M S. Rodrigues, Charlie Basset, Lionel Chevolut, Romain Girod, Christian Moretti, Didier Stien, Isabelle Dusfour and Véronique Eparvier	1319
Phenolic Compounds in Five <i>Epilobium</i> Species Collected from Estonia Indrek Rimmel, Lauri Vares, Lauri Toom, Vallo Matto and Ain Raal	1323
A New Prenylated Acetophenone from the Root Bark of <i>Derris indica</i> Naushad Edayadulla and Penugonda Ramesh	1325
Phytotoxic Furanocoumarins from the Shoots of <i>Semenovia transiliensis</i> Shobha Sondhia, Stephen O. Duke, Solomon Green III, Nadezhda G. Gemejyeva, Leonid K. Mamonov and Charles L Cantrell	1327
Chemoenzymatic Synthesis of Two New Halogenated Coumarin Glycosides as Potential Antifungal Agents Liangbin Zhou, Ling Liu, Tian Tian, Bailin Xue and Rongmin Yu	1331
Two New Naphthoquinone Derivatives from the Stem Bark of <i>Callicarpa maingayi</i> Sumayah Mohammed Asiri, Khozirah Shaari, Faridah Abas, Nabil Ali Al-Mekhlafi and Nordin H. Lajis	1333
Novel Sorbicillin Analogues from the Marine Fungus <i>Trichoderma</i> sp. Associated with the Seastar <i>Acanthaster planci</i> Wen-Jian Lan, Yang Zhao, Zhong-Liang Xie, Li-Zhen Liang, Wei-Yan Shao, Long-Ping Zhu, De-Po Yang, Xiao-Feng Zhu and Hou-Jin Li	1337
Cytotoxic Bioactivity of some Phenylpropanoic Acid Derivatives Guillermo F. Reta, Carlos E. Tonn, Carla Ríos-Luci, Leticia G. León, Eduardo Pérez-Roth, José M. Padrón, and Osvaldo J. Donadel	1341
Anti-<i>Helicobacter pylori</i> Activities of Natural Isopentenylloxycinnamyl Derivatives from <i>Boronia pinnata</i> Cécile Ribeiro da Silva, Valérie Michel, Salvatore Genovese, Marie-Christine Prévost, Francesco Epifano and Eliette Touati	1347

Continued inside backcover