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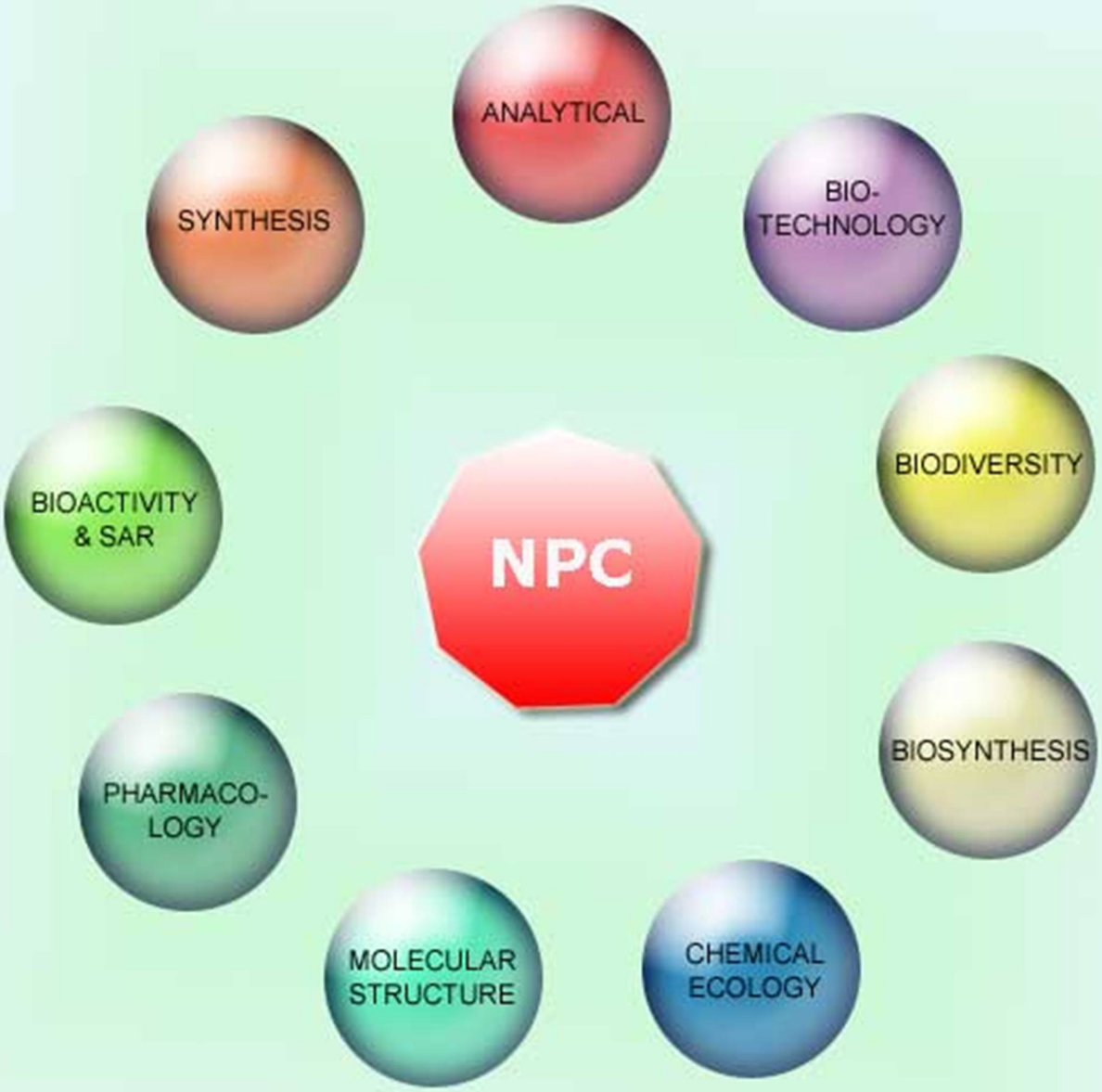

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Cytotoxic Bioactivity of some Phenylpropanoic Acid Derivatives

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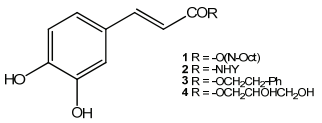
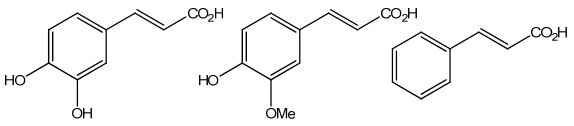
In this study, we synthesized a series of phenylpropanoic acid derivatives based on modifications at four selected points of the molecular scaffold. The *in vitro* antiproliferative activities of the compounds were examined in representative human solid tumor cell lines. A SAR was established pointing out the relevance of the substituents. The best activity profiles were obtained for the derivatives bearing more lipophilic esters (GI_{50} 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.





5 **6** **7**

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 CH_2N_2 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 CH_2N_2 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

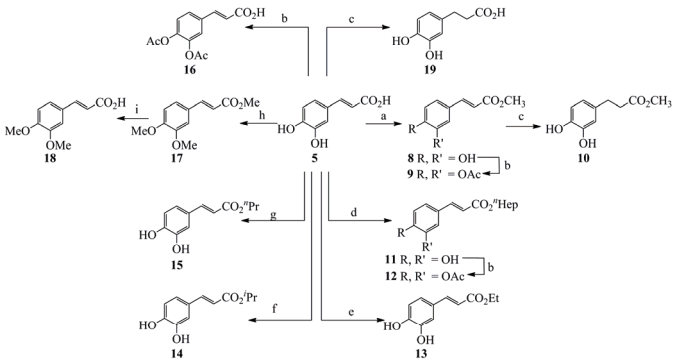


Figure 1: Reagents and conditions: a) CH_2N_2, Et_2O, 81%; b) Ac_2O, DMAP, Py, 85% for **9**, 76% for **12**, 78% for **16**; c) H_2, Pd/C, 1 atm, AcOEt, 75% for **10**, 88% for **19**; d) DCC, DMAP, *n*-heptanol, 66%; e) $(CH_3)_3SiCl$, EtOH, 93%; f) HCl, i-PrOH, 60%; g) HCl, *n*-PrOH, 72%; h) Me_2SO_4, K_2CO_3, NaF, acetone, 78%; i) KOH, H_2O, 54%.

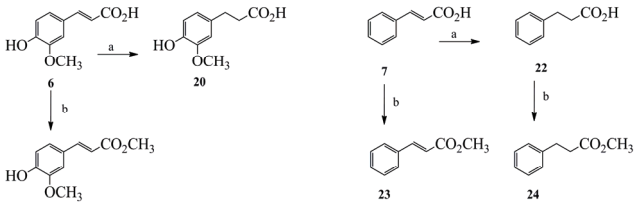


Figure 2: Reagents and conditions: a) H_2, Pd/C, 1 atm, AcOEt, 83% for **20**, 95% for **22**; b) CH_2N_2, Et_2O, 84% for **21**, 79% for **23**, 85% for **24**.

that should be globally associated with drug solubility and drug permeability through cell membranes 0. 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 Clog*P* (calculated log *P*) or Mlog*P* (Moriguchi log *P*) if the Hansch–Leo's fragment constant method 0 or Moriguchi's method 0 are used, respectively. However, Clog*P* values are more accurate than Mlog*P* values. There exist several computer programs that calculate the Clog*P* values 0, with Clog*P*® the more accurate predictor and the one chosen for our study 0.

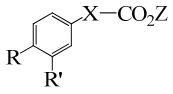
The Clog*P* values for compounds **5**-**24** were in the range 0.64 to 4.38 and are given in Table 1. Clog*P* values were calculated to correlate lipophilicity with the biological activity. Overall, a direct correlation between lipophilicity of the side chain (Z) and antiproliferative activity was obtained.

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 (GI_{50} > 100 μM) 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 ≈ *i*-Pr ≈ 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** ≈ **9**, **11** ≈ **12**, **5** >= **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	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	*n*-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	*n*-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*-Pr	16 (±3.3)	14 (±6.4)	13 (±2.9)	42 (±4.0)	28 (±7.2)
15	2.26	OH	OH	CH=CH	*n*-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 0ºC 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%.
^{1}H NMR (200 MHz, CD_3OD): 3.80 (3H, s, -OCH_3), 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). ^{13}C NMR (50.23 MHz, CD_3OD) in full agreement with the literature.
Anal. Calcd for $C_{10}H_{10}O_4$: 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 Na_2SO_4. 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%.
^{1}H NMR (200MHz, CD_3OD): 2.30 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.80 (3H, s, -OCH_3), 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 $C_{14}H_{14}O_6$: 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%.
^{1}H NMR (400 MHz, $CDCl_3$): 2.62 (2H, t, J = 7 Hz, H-8), 2.85 (2H, t, J = 7 Hz, H-7), 3.70 (3H, s, -OCH_3), 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).
^{13}C NMR (100.5 MHz, $CDCl_3$): 30.25 (CH_2), 35.95 (CH_2), 51.87 (CH_3), 115.38 (2 CH), 120.48 (CH), 133.17 (C), 142.14 (C), 143.67 (C), 174.28 (C).
Anal. Calcd for $C_{10}H_{12}O_4$: 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 Na_2SO_4, 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%.
^{1}H NMR (400 MHz, CD_3OD): 0.93 (3H t, J = 6 Hz, CH_3, ^{n}Hep side chain), 1.39-1.30 (8H m 4 CH_2 ^{n}Hep side chain), 1.70 (2H, m, CH_2 ^{n}Hep side chain), 4.17 (2H, t, J = 6.8 Hz, –OCH_2- *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).
^{13}C NMR (100.5 MHz, CD_3OD): 13.01 (CH_3, ^{n}Hep side chain); 22.25 (CH_2, ^{n}Hep side chain); 25.66 (CH_2, ^{n}Hep side chain); 28.47 (CH_2, ^{n}Hep side chain); 28.68 (CH_2, ^{n}Hep side chain); 31.51 (CH_2, ^{n}Hep side chain); 64.18 (CH_2, ^{n}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 $C_{16}H_{22}O_4$: 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 Na_2SO_4, 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%.
^{1}H NMR (200 MHz, $CDCl_3$): 0.92 (3H, t, J = 6.2 Hz, –OCH_3, ^{n}Hep side chain); 1.25-1.34 (8H, m, CH_2, ^{n}Hep side chain); 1.68 (2H, m, CH_2, ^{n}Hep side chain); 2.30 (6H, s, -$OCOCH_3$); 4.19 (2H, t, J = 6.3 Hz, CH_2, ^{n}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).
^{13}C NMR (50.23 MHz, $CDCl_3$): 13.8 (CH_3, ^{n}Hep side chain); 22.4*, 25.6*, 28.6*, 31.4* (CH_2, ^{n}Hep side chain); 28.5 (CH_2, ^{n}Hep side chain); 20.4 ($OCOCH_3$); 64.6 (–OCH_2, ^{n}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 (-$OCOCH_3$).
Anal. Calcd for $C_{20}H_{26}O_6$: 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%.

^{1}H NMR (400 MHz, CD_3OD): 1.32 (3H, t, J = 7.2 Hz, CH_3, side chain), 4.23 (2H, c, J = 7.2 Hz, CH_2, 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).

^{13}C NMR (100.5 MHz, CD_3OD): 13.23 (CH_3, side chain); 60.02 (-OCH_2, 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 $C_{11}H_{12}O_4$: 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 Na_2SO_4. 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%.

^{1}H NMR (400 MHz, CD_3OD): 1.30 (6H, d, J = 6.4 Hz, CH_3, 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).

^{13}C NMR (100.5 MHz, CD_3OD): 20.77 (CH_3, 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 $C_{12}H_{14}O_4$: 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 Na_2SO_4. 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%.

^{1}H NMR (400 MHz, CD_3OD): 1.01 (3H, t, J = 7.2 Hz, CH_3, side chain), 1.73 (2H, m, CH_2, side chain), 4.14 (2H, t, J = 6.4 Hz, -OCH_2, 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).

^{13}C NMR (100.5 MHz, CD_3OD): 9.34 (CH_3, side chain); 21.77 (CH_2, side chain); 65.66 (OCH_2, 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 $C_{12}H_{14}O_4$: 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%.

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

Anal. Calcd for $C_{13}H_{12}O_6$: 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), K_2CO_3 (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 $NaHCO_3$, and then dried with anhydrous Na_2SO_4, filtered and concentrated; 192 mg of **17** was obtained as yellow oil. Yield: 78%.

^{1}H NMR (200 MHz, $CDCl_3$ and CD_3OD): 3.77 (3H, s, -$COOCH_3$), 3.88 (3H, s, -OCH_3), 3.89 (3H, s, -OCH_3), 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).

^{13}C NMR (50.25 MHz, $CDCl_3$ and CD_3OD): 51.0 (-$COOCH_3$); 55.3 (-O*CH_3); 55.4 (-O*CH_3); 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 $C_{12}H_{14}O_4$: 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 Na_2SO_4, 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%.

^{1}H NMR (400 MHz, $CDCl_3$): 3.92 (6H, s, -OCH_3), 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).

^{13}C NMR (100.5 MHz, $CDCl_3$): 55.9 (-OCH_3*), 56.0 (-OCH_3*), 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 $C_{11}H_{12}O_4$: 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%.

^{1}H 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).

^{13}C NMR (100.5 MHz, $CDCl_3$): 30.5 (CH_2), 35.6 (CH_2), 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%.
^{1}H 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 (CH_2), 35.95 (CH_2), 55.87 (-OCH_3);, 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-methoxy-phenyl)acrylate (21): To a stirred solution of ferulic acid (**6**) (100 mg, 0.52 mmol) in anhydrous diethyl ether (50 mL) at 0ºC 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%.
^{1}H NMR (400 MHz, CD_3OD): 3.80 (3H, s, -$COOCH_3$); 3.90 (3H, s, -OCH_3); 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 (-$COOCH_3$); 55.8 (-OCH_3); 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%.
^{1}H 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 (CH_2); 35.59 (CH_2); 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 0ºC 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%.
^{1}H NMR (400 MHz, $CDCl_3$): 3.83 (3H, s, -OCH_3), 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 0ºC 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%.
^{1}H 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, -OCH_3); 7.17-7.28 (5H, m, H2-H6).
^{13}C NMR ($CDCl_3$, 100.5 MHz): 30.9 (CH_2); 35.7 (CH_2); 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 μM.

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 cm^2 culture flasks in RPMI 1640 supplemented with 5% FBS and 2 mM L-glutamine in a 37ºC, 5% CO_2, 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 μL 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 μM. The drug treatment was started on day 1 after plating. Drug incubation time was 48 h, after which time cells were precipitated with 25 μL ice-cold TCA (50%, w/v) and fixed for 60 min at 4ºC. Then the SRB assay 0 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 × [(T-T_0)/(C-T_0)]. If T is less than T_0 denoting cell killing the calculation is PG = 100 × [(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.

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