Supplementary Material

Hydroxytyrosol (HT) analogs act as potent antifungals by direct disruption of the fungal cell membrane

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**Supplementary Data**

**Experimental**

Melting points were determined on a Büchi apparatus and are uncorrected. 1H NMR spectra and 2D spectra were recorded on a Bruker Avance III 600 or a Bruker Avance DRX 400 instrument, whereas 13C NMR spectra were recorded on a Bruker Avance III 600 or a Bruker AC 200 spectrometer in deuterated solvents and were referenced to TMS (d scale). The signals of 1H and 13C spectra were unambiguously assigned by using 2D NMR techniques: COSY, NOESY, HMQC, and HMBC. Mass spectra were recorded with a LTQ Orbitrap Discovery instrument, possessing an Ionmax ionization source. Flash chromatography was performed on Merck silica gel 60 (0.040-0.063 mm). Analytical thin layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates.

**General Procedure for the synthesis of compounds 2-12**

Sodium hydride (260 mg, 6.52 mmol, 60% in paraffin oil) was added at 0 °C, under argon to a solution of the appropriate acid (3.26 mmol) in dry DMF (20 mL) and the reaction mixture was stirred at room temperature for 5 min. The reaction was then cooled to 0 °C, a solution of 2-Chloro-3′,4′-dihydroxyacetophenone (0.91 g, 4.89 mmol) in DMF (2 mL) was added dropwise and the mixture was stirred at 70 °C for 4-8 h. After completion of the reaction, the volatiles were vacuum evaporated, the resulting residue was dissolved in ethyl acetate (60 mL) and washed with water (3 x 20 mL), saturated NaCl solution, dried (anhydrous Na2SO4) and evaporated to dryness. The residue was purified by column chromatography to afford the title compounds.

2-(3,4-dihydroxyphenyl)-2-oxoethyl adamantane-1-carboxylate (**2**).

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **2** in73% yield.

Mp: 172-173 °C (Ethanol). 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.00 (br s, 1H, D2O exchang., 3’-O*H*), 9.45 (br s, 1H, D2O exchang., 4’-O*H*), 7.35 (d, *J* = 8.2 Hz, 1H, H-6’), 7.31 (s, 1H, H-2’), 6.84 (d, *J* = 8.2 Hz, 1H, H-5’), 5.31 (s, 2H, C*H*2O), 2.04-1.96 (m, 3H, C*H* adamantyl), 1.95-1.86 (m, 6H, C*H*2 adamantyl), 1.78-1.60 (m, 6H, C*H*2 adamantyl). 13C NMR (151 MHz, DMSO-*d6*) δ (ppm): 190.70 (*C*OCH2), 175.96 (O*C*O), 151.23 (C-4’), 145.39 (C-3’), 125.86 (C-1’), 120.98 (C-6’), 115.16 (C-5’), 114.47 (C-2’), 65.56 (*C*H2O), 39.99 (C adamantyl), 38.46 (*C*H2 adamantyl), 35.94 (*C*H2 adamantyl), 27.29 (*C*H adamantyl). HR-MS (ESI) m/z: Calcd for C19H21O5: [M1 - H]- = 329.1394, found 329.1386.

2-(3,4-dihydroxyphenyl)-2-oxoethyl 3,5-dihydroxy benzoate (**3**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (1/1) as the eluent, affording the corresponding ester **3** in64% yield.

Mp: 275-276 °C (Dec.) (EtOAc). 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 9.76 (br s, 4H, D2O exchang., 3-O*H*, 5-O*H*, 3-O*H*’, 4’-O*H*), 7.41 (d, *J* = 8.3 Hz, 1H, H-6’), 7.36 (s, 1H, H-2’), 6.89 (s, 2H, H-2, H-6), 6.87 (d, *J* = 8.3 Hz, 1H, H-5’), 6.49 (s, 1H, H-4), 5.55 (s, 2H, C*H*2O). 13C NMR (151 MHz, DMSO-*d6*) δ (ppm): 190.75 (*C*OCH2), 165.40 (O*C*O), 158.64 (C-3, C-5), 151.45 (C-4’), 145.55 (C-3’), 131.07 (C-1), 125.88 (C-1’), 121.19 (C-6’), 115.34 (C-5’), 114.58 (C-2’), 107.48 (C-4), 107.38 (C-2, C-6), 66.54 (*C*H2O). HR-MS (ESI) m/z: Calcd for C15H11O7: [M1 - H]- = 303.0510, found 303.0500.

2-(3,4-dihydroxyphenyl)-2-oxoethyl octanoate (**4**)

The crude product was purified by column chromatography (silica gel) using a mixture cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **4** in78% yield.

Mp: 105-106 °C (Et2O/n-hexane). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.58 (d, *J* = 2.0 Hz, 1H, H-2’), 7.41 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6’), 6.93 (d, *J* = 8.3 Hz, 1H, H-5’), 5.35 (s, 2H, C*H*2O), 2.53 (t, *J* = 7.6 Hz, 2H, 2-C*H*2), 1.76–1.66 (m, 2H, 3-C*H*2), 1.42–1.24 (m, 8H, 4-C*H*2, 5-C*H*2, 6-C*H*2, 7-C*H*2), 0.90 (t, *J* = 7.6 Hz, 3H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 191.67 (*C*OCH2), 174.46 (O*C*OCH2), 150.29 (C-4’), 143.86 (C-3’), 126.94 (C-1’), 122.43 (C-6’), 114.97 (C-5’), 114.61 (C-2’), 65.83 (*C*H2O), 34.02 (C-2), 31.63 (C-6), 29.06 (C-5), 28.91 (C-4), 24.85 (C-3), 22.59 (C-7), 14.05 (C-8). HR-MS (ESI) m/z: Calcd for C16H21O5: [M1 - H]- = 293.1394, found 293.1386.

2-(3,4-dihydroxyphenyl)-2-oxoethyl 2-(adamantan-1-yl)acetate (**5**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (2/1) as the eluent, affording the corresponding ester **5** in88% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 7.54 (d, *J* = 2.0 Hz, 1H, H-2’), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6’), 7.03 (br s, 1H, D2O exchang., 3’-O*H*), 6.90 (d, *J* = 8.3 Hz, 1H, H-5’), 6.40 (br s, 1H, D2O exchang., 4’-O*H*), 5.30 (s, 2H, C*H*2O), 2.26 (s, 2H, C*H2*CO), 1.98 (m, 3H, C*H* adamantyl), 1.74–1.59 (m, 12H, C*H*2 adamantyl). 13C NMR (151 MHz, CDCl3) δ (ppm): 191.77 (*C*OCH2), 172.39 (O*C*OCH2), 150.34 (C-4’), 143.98 (C-3’), 127.22 (C-1’), 122.56 (C-6’), , 115.10 (C-5’), 114.77 (C-2’), 65.81 (*C*H2O), 48.74 (*C*H2CO), 42.45 (*C*H2 adamantyl), 36.83 (*C*H2 adamantyl), 33.17 (C adamantyl), 28.77 (*C*H adamantyl). HR-MS (ESI) m/z: Calcd for C20H22O5: [M1 - H]- = 343.1550, found 343.1546.

(E)-2-(3,4-dihydroxyphenyl)-2-oxoethyl 3-(4-hydroxy-3-methoxyphenyl)acrylate (**6**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (1/5) as the eluent, affording the corresponding ester **6** in75% yield.

1H NMR (600 MHz, CDCl3-MeOD) δ (ppm): 7.62 (d, *J* = 15.9 Hz, 1H, COCH=C*H*), 7.40 (d, *J* = 2.0 Hz, 1H, H-2’), 7.38 (dd, *J* = 8.3 Hz, 2.0 Hz, 1H, H-6’), 7.03-7.06 (m, 2H, H-2, H- 6), 6.83-6.87 (m, 2H, H-5, H-5’), 6.33 (d, *J* = 15.8 Hz, 1H, COC*H*=CH), 5.30 (s, 2H, C*H*2O), 3.82 (s, 3H, OC*H*3). 13C NMR (151 MHz, CDCl3--MeOD) δ (ppm): 193.11 (*C*OCH2), 168.28 (O*C*OCH), 152.48 (C-4’), 150.29 (C-4), 148.95 (C-5), 147.42 (C-3’), 146.32 (COCH=*C*H), 127.37 (C-1’), 127.29 (C-1), 124.02 (C-6’), 122.44 (C-2), 116.23 (C-5’), 115.83 (CO*C*H=CH), 115.38 (C-3), 114.44 (C-2’), 111.41 (C-6), 66.70 (*C*H2O), 56.32 (O*C*H3). HR-MS (ESI) m/z: Calcd for C18H15O7: [M1 - H]- = 343.0823, found 343.0817.

(E)-2-(3,4-dihydroxyphenyl)-2-oxoethyl docos-13-enoate (**7**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **7** in76% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 7.55 (d, *J* = 2.0 Hz, 1H, H-2’), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6’), 6.91 (d, *J* = 8.3 Hz, 1H, H-5’), 6.83 (br s, 1H, D2O exchang., 3’-O*H*), 6.26 (br s, 1H, D2O exchang., 4’-O*H*), 5.38–5.32 (m, 2H, C*H*=C*H*), 5.31 (s, 2H, C*H*2O), 2.51 (t, *J* = 7.6 Hz, 2H, COC*H*2), 2.04–1.98 (m, 4H, 12-C*H*2, 15-C*H*2), 1.70 (m, 2H, 3-C*H*2), 1.40–1.17 (m, 28H, C*H*2 erucic), 0.88 (t, *J* = 7.0 Hz, 3H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 191.56 (*C*OCH2), 174.36 (O*C*OCH2), 150.26 (C-4’), 143.93 (C-3’), 130.06 (*C*H=*C*H), 127.25 (C-1’), 122.56 (C-6’), 115.11 (C-5’), 114.74 (C-2’), 65.92 (*C*H2O), 34.17 (C-2), 32.06 (C-20), 29.93 (*C*H2erucic), 29.86 (*C*H2 erucic), 29.77 (*C*H2 erucic), 29.76 (*C*H2 erucic), 29.72 (*C*H2 erucic), 29.68 (*C*H2 erucic), 29.61 (*C*H2 erucic), 29.47 (*C*H2 erucic), 29.42 (*C*H2 erucic), 29.28 (*C*H2 erucic), 27.37 (C-12, C-15), 25.02 (C-3), 22.83 (C-21), 14.26 (*C*H3). HR-MS (ESI) m/z: Calcd for C30H47O5: [M1 - H]- = 487.3429, found 487.3420.

(E)-2-(3,4-dihydroxyphenyl)-2-oxoethyl penta-2,4-dienoate (**8**)

The crude product was purified by column chromatography (silica gel) using a mixture of CH2Cl2 / MeOH (100/0.75) as the eluent, affording the corresponding ester **8** in80% yield.

1H NMR (600 MHz, Acetone-*d*6) δ δ (ppm): 7.31-7.37 (m, 2H, H-2’, H-6’), 7.18 (m, 1H, COCH=C*H*), 6.83 (d, *J* = 8.3 Hz, 1H, H-5’), 6.25–6.09 (m, 2H, COC*H*=CH, CH3CH=C*H*), 5.82 (m, 1H, CH3C*H*=CH), 1.73 (t, *J* = 5.1 Hz, 1H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 191.28 (*C*OCH2), 166.70 (O*C*OCH), 151.62 (C-4’), 146.42 (*C*H sorbic), 146.11 (C-3’), 140.57 (*C*H sorbic), 130.69 (*C*H sorbic), 128.05 (C-1’), 122.21 (C-6’), 119.28 (*C*H sorbic), 115.91 (C-5’), 115.33 (C-2’), 66.49 (*C*H2O), 18.69 (*C*H3). HR-MS (ESI) m/z: Calcd for C14H13O5: [M1 - H]- = 261.0768, found 261.0770.

2-(3,4-dihydroxyphenyl)-2-oxoethyl 4-methylenecyclohexanecarboxylate (**9**)

The crude product was purified by column chromatography (silica gel) using a mixture of CH2Cl2 / MeOH (100/1.5) as the eluent, affording the corresponding ester **9** in85% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 7.51 (d, *J* = 2.0 Hz, 1H, H-2’), 7.40 (dd, *J* = 8.3, 2.1 Hz, 1H, H-6’), 6.91 (d, *J* = 8.3 Hz, 1H, H-5’), 6.60 (br s, 1H, D2O exchang., 3’-O*H*), 6.30 (br s, 1H, D2O exchang., 4’-O*H*), 5.30 (s, 2H, C*H*2O), 4.67 (s, 2H, C*H2=*C, 2.67 (m, 1H, COC*H*), 2.44–2.35 (m, 2H, C*H* cyclohexyl), 2.14–2.07 (m, 4H, C*H* cyclohexyl), 1.73–1.64 (m, 2H, C*H* cyclohexyl). 13C NMR (151 MHz, CDCl3) δ (ppm): 191.23 (*C*OCH2), 175.67 (O*C*OCH), 150.08 (C-4’) ,147.60 (*C*=CH2), 143.91 (C-3’), 127.40 (C-1’), 122.51 (C-6’),115.09 (C-5’),114.69 (C-2’), 108.24 (C=*C*H2), 68.16 (*C*HCO), 65.84 (*C*H2O), 42.53(C cyclohexyl), 33.70 (C cyclohexyl), 30.26(C cyclohexyl), 25.76 (C cyclohexyl). HR-MS (ESI) m/z: Calcd for C16H17O5: [M1 - H]- = 289.1081, found 289.1079.

2-(3,4-dihydroxyphenyl)-2-oxoethyl 4-isopropylcyclohexanecarboxylate (**10**)

The crude product was purified by column chromatography (silica gel) using a mixture of CH2Cl2 / MeOH (100/1) as the eluent, affording the corresponding ester **10** in78% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): δ 7.38 (d, *J* = 2.0 Hz, 1H, H-2’), 7.29 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6’), 6.80 (d, *J* = 8.3 Hz, 1H, H-5’), 5.29 – 5.20 (m, 2H, C*H*2O), 2.46 (m, 1H, CH), 2.26 (m, 1H, CH), 2.14 – 1.98 (m, 1H, CH), 1.23 (m, 1H, CH), 1.11 (m, 1H, CH), 1.04-0.98 (m, 3H, CH3), 0.87 (d, *J* = 1.9 Hz, 9H, CH3). 13C NMR (151 MHz, CDCl3) δ (ppm): δ 192.06 (*C*OCH2), 173.51 (O*C*OCH2), 150.69 (C-4’), 144.53 (C-3’), 126.70 (C-1’), 122.13 (C-6’), 115.03 (C-5’), 114.60 (C-2’), 65.75 (*C*H2O), 50.61 (*C*H2CH), 43.58 (*C*H2CO), 31.06 (C), 29.96 (3xC*H*3), 27.03 (*C*H), 22.60 (C*H*3). HR-MS (ESI) m/z: Calcd for C18H23O5: [M1 - H]- = 319.1551, found 319.1542.

2-(3,4-dihydroxyphenyl)-2-oxoethyl 3,5,5-trimethylhexanoate (**11**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / CH2Cl2 (1/10) as the eluent, affording the corresponding ester **11** in89% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 7.38 (d, J = 2.0 Hz, 1H, H-2’), 7.29 (dd, *J* = 8.3, 2.0 Hz, 1H, H-6’), 6.80 (d, *J* = 8.3 Hz, 1H, H-5’), 5.29–5.20 (m, 2H, C*H*2O), 2.46 (m, 1H, C*H*), 2.26 (m, 1H, C*H*), 2.14–1.98 (m, 1H, C*H*), 1.23 (m, 1H, C*H*), 1.11 (m, 1H, C*H*), 1.04-0.98 (m, 3H, C*H*3), 0.87 (d, J = 1.9 Hz, 9H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 192.06 (*C*OCH2), 173.51 (O*C*OCH2), 150.69 (C-4’), 144.53 (C-3’), 126.70 (C-1’), 122.13 (C-6’), 115.03 (C-5’), 114.60 (C-2’), 65.75 (*C*H2O), 50.61 (C-4), 43.58 (C-2), 31.06 (C-5), 29.96 (*C*H3), 26.99 (C-3), 22.60 (*C*H3). HR-MS (ESI) m/z: Calcd for C17H23O5: [M1 - H]- = 307.1550, found 307.1540.

2-(3,4-dihydroxyphenyl)-2-oxoethyl 2-cyclohexylacetate (**12**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **12** in95% yield, as an oil.

1H NMR (400 MHz, CDCl3) δ (ppm): 6.81 (d, *J* = 8.0 Hz, 1H, H-5’), 6.75 (d, *J* = 1.8 Hz, 1H, H-2’), 6.62 (dd, *J* = 8.0, 1.8 Hz, 1H, H-6’), 4.27 (t, *J* = 7.0 Hz, 2H, CH2C*H*2O), 2.84 (t, *J* = 7.0 Hz, 2H, C*H*2CH2O), 2.19 (d, *J* = 7.1 Hz, 2H, COC*H*2), 1.82–1.60 (m, 6H, H-1, H-2, H-3, H-4, H-5, H-6), 1.31–1.08 (m, 3H, H-3, H-4, H-5), 0.98–0.91 (m, 2H, H-2, H-6). 13C NMR (151 MHz, CDCl3) δ (ppm):174.33 (*C*O), 143.89 (C-3’), 142.58 (C-4’), 130.18 (C-1’), 121.07 (C-6’), 115.83 (C-5’), 115.31 (C-2’), 65.23 (CH2*C*H2O), 42.29 (CO*C*H2), 34.89 (*C*H2CH2O), 34.41 (C-1), 32.94 (C-2, C-6), 26.90 (C-4), 26.06 (C-3, C-5). HR-MS (ESI) m/z: Calcd for C16H19O5: [M1 - H]- = 291.1237, found 291.1237.

**General Procedure for the synthesis of compounds 13-20**

Triethylsilane (0.312 mL, 1.96 mmol) was added dropwise to a suspension of the appropriate ester **2**-**12** (0.49 mmol) in trifluoroacetic acid (0.190 mL, 2.45 mmol), at 0 °C. The flask was sealed and the resulting mixture was stirred at room temperature for 3-6 h. After completion of the reaction, the volatiles were vacuum evaporated, the resulting residue was dissolved in ethyl acetate (40 mL) and washed with water (3 x 15 mL), saturated NaCl solution, dried (anhydrous Na2SO4) and evaporated to dryness.

3,4-dihydroxyphenethyl adamantane-1-carboxylate (**13**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **13** in77% yield.

Mp: 151-152 °C (c-Hex). 1H NMR (400 MHz, DMSO-*d6*) δ (ppm):8.78 (br s, 1H, D2O exchang, 4’-O*H*), 8.69 (br s, 1H, D2O exchang, 3’-O*H*), 6.64 (d, *J* = 7.9 Hz, 1H, H-5’), 6.61 (d, *J* = 1.5 Hz, 1H, H-2’), 6.46 (dd, *J* = 7.9, 1.5 Hz, 1H, H-6’), 4.10 (t, *J* = 6.8 Hz, 2H, CH2C*H*2O), 2.68 (t, *J* = 6.8 Hz, 2H, C*H*2CH2O), 2.01-1.90 (m, 3H, C*H* adamantyl), 1.81-1.73 (m, 6H, C*H*2 adamantyl), 171-1.60 (m, 6H, C*H*2 adamantyl). 13C NMR (50 MHz, DMSO-*d6*) δ (ppm):176.83 (*C*O), 145.48 (C-3’), 143.92 (C-4’), 129.12 (C-1’), 119.98 (C-6’), 116.72 (C-2’), 115.88 (C-5’), 64.83 (CH2*C*H2O), 40.00 (C adamantyl), 38.82 (*C*H2 adamantyl), 36.39 (*C*H2 adamantyl), 34.32 (*C*H2CH2O), 27.76 (*C*H adamantyl). HR-MS (ESI) m/z: Calcd for C19H23O4: [M1 - H]- = 315.1601, found 315.1599.

3,4-dihydroxyphenethyl 3,5-dihydroxy benzoate (**14**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (1/1) as the eluent, affording the corresponding ester **14** in84% yield.

Mp: 110-111 °C (EtOAc- c-Hex). 1H NMR (600 MHz, DMSO-*d6*) δ (ppm): 9.64 (br s, 2H, D2O exchang, 3-O*H* ,5-O*H*), 8.79 (br s, 1H, D2O exchang, 4’-O*H*), 8.75 (br s, 1H, D2O exchang, 3’-O*H*), 6.80 (d, *J* = 2.1 Hz, 2H, H-2, H-6), 6.67 (d, *J* = 7.9 Hz, 1H, H-5’), 6.64 (d, *J* = 2.1 Hz, 1H, H-2’), 6.53 (dd, *J* = 7.9, Hz, 2.1 Hz, 1H, H-6’), 6.44 (t, *J* = 2.3 Hz, 1H, H-4), 4.32 (t, *J* = 6.8 Hz, 2H, CH2C*H*2O), 2.81 (t, *J* = 6.8 Hz, 2H, C*H*2CH2O). 13C NMR (151 MHz, DMSO-*d6*) δ (ppm): 166.28 (*C*O), 158.82 (C-3, C-5), 145.65 (C-3’), 144.32 (C-4’), 132.03 (C-1), 129.25 (C-1’), 119.84 (C-6’), 116.78 (C-2’), 116.11 (C-5’), 107.55 (C-2, C-4, C-6), 66.04 (CH2*C*H2O), 34.37 (*C*H2CH2O). HR-MS (ESI) m/z: Calcd for C15H13O6: [M1 - H]- = 289.0717, found 289.0713.

3,4-dihydroxyphenethyl octanoate (**15**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **15** in91% yield, as an oil.

1H NMR (400 MHz, CDCl3) δ (ppm): 6.81 (d, *J* = 8.0 Hz, 1H, H-5’), 6.75 (d, *J* = 1.6 Hz, 1H, H-2’), 6.62 (dd, *J* = 8.0, 1.6 Hz, 1H, H-6’), 4.26 (t, *J* = 7.2 Hz, 2H, CH2C*H*2O), 2.82 (t, *J* = 7.2 Hz, 2H, C*H*2CH2O), 2.32 (t, *J* = 7.2 Hz, 2H, 2-C*H*2), 1.66–1.57 (m, 2H, 3-C*H*2), 1.22-1.36 (m, 8H, 4-C*H*2, 5-C*H*2, 6-C*H*2, 7-C*H*2), 0.90 (t, *J* = 7.2 Hz, 3H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm):175.01 (*C*O), 143.80 (C-3’), 142.50 (C-4’), 130.31 (C-1’), 121.19 (C-6’), 115.86 (C-2’), 115.36 (C-5’), 65.28 (CH2*C*H2O), 34.47 (*C*H2CH2O), 34.42 (C-2), 31.63 (C-6), 29.05 (C-5), 28.89 (C-4), 24.94 (C-3), 22.59 (C-7), 14.05 (C-8). HR-MS (ESI) m/z: Calcd for C16H23O4: [M1 - H]- = 279.1601, found 279.1590.

3,4-dihydroxyphenethyl 2-(adamantan-1-yl)acetate (**16**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **16** in95% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 6.79 (d, *J* = 8.1 Hz, 1H, H-5’), 6.75 (d, *J* = 2.0 Hz, 1H, H-2’), 6.63 (dd, *J* = 8.1, 2.0 Hz, 1H, H-6’), 4.24 (t, *J* = 7.1 Hz, 2H, CH2C*H*2O), 2.82 (t, *J* = 7.1 Hz, 2H, C*H*2CH2O), 2.06 (s, 2H, C*H2*CO), 1.93 (m, 3H, C*H* adamantyl), 1.70–1.57 (m, 6H, C*H*2 adamantyl), 1.54 (m, 6H, C*H*2 adamantyl). 13C NMR (151 MHz, CDCl3) δ (ppm): 172.66 (*C*O), 143.72 (C-3’), 142.41 (C-4’), 130.51 (C-1’), 121.25 (C-6’), 115.85 (C-2’), 115.30 (C-5’), 64.88 (CH2*C*H2O), 49.14 (*C*H2CO), 42.39 (*C*H2 adamantyl), 36.68 (*C*H2 adamantyl), 34.47 (*C*H2CH2O), 32.82 (C adamantyl), 28.61 (*C*H adamantyl). HR-MS (ESI) m/z: Calcd for C20H25O4: [M1 - H]- = 329.1758, found 329.1749.

(Z)-3,4-dihydroxyphenethyl docos-13-enoate (**17**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **17** in95% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 6.78 (d, *J* = 8.0 Hz, 1H, H-5’), 6.73 (d, *J* = 2.0 Hz, 1H, H-2’), 6.63 (dd, *J* = 8.0, 2.0 Hz, 1H, H-6’), 5.35 (m,2H, C*H*=C*H*), 4.24 (t, *J* = 7.1 Hz, 2H, CH2C*H*2O), 2.81 (t, *J* = 7.1 Hz, 2H, C*H*2CH2O), 2.29 (t, *J* = 7.6 Hz, 2H, COC*H*2), 2.01 (m, 4H, 12-C*H*2, 15-C*H*2), 1.61 (m, 2H, 3-C*H*2), 1.38–1.17 (m, 28H, C*H*2 erucic), 0.88 (t, J = 6.9 Hz, 3H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 174.58 (*C*O), 143.81 (C-3’), 142.46 (C-4’), 130.74 (C-1’), 130.06 (*C*H=*C*H), 121.42 (C-6’), 116.02 (C-2’), 115.49 (C-5’), 65.18 (CH2*C*H2O), 34.58 (*C*H2CH2O), 33.82 (C-2), 32.00 (C-20), 30.24–28.81 (*C*H2 erucic), 27.37 (C-12, C-15), 25.02 (C-3), 22.81 (C-21), 14.24 (*C*H3). HR-MS (ESI) m/z: Calcd for C30H49O4: [M1 - H]- = 473.3636, found 473.3636.

3,4-dihydroxyphenethyl 4-isopropylcyclohexanecarboxylate (**18**)

The crude product was purified by column chromatography (silica gel) using a mixture of CH2Cl2 / MeOH (100/1) as the eluent, affording the corresponding ester **18** in96% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 6.78 (d, *J* = 8.1 Hz, 1H, H-5’), 6.73 (d, *J* = 2.0 Hz, 1H, H-2’), 6.63 (dd, *J* = 8.1, 2.0 Hz, 1H, H-6’), 5.60 (br s, 1H, D2O exchang., 4’-O*H*), 5.40 (br s, 1H, D2O exchang., 3’-O*H*), 4.22 (t, *J* = 7.1 Hz, 2H, CH2C*H*2O), 2.81 (t, *J* = 7.1 Hz, 2H, C*H*2CH2O), 2.25 – 2.14 (m, 1H, C*H*), 1.98 – 1.93 (m, 2H, C*H*), 1.80 – 1.73 (m, 2H, C*H*), 1.44 – 1.32 (m, 3H, C*H*), 1.06 – 0.93 (m, 3H, C*H*), 0.85 (d, *J* = 6.8 Hz, 6H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 176.82 (*C*O), 143.77 (C-3’), 142.39 (C-4’), 130.90 (C-1’), 121.47 (C-6’), 116.05 (C-2’), 115.46 (C-5’), 65.02 (CH2*C*H2O), 43.80 (*C*H), 43.42 (*C*H), 34.64 (*C*H2CH2O), 32.91 (*C*H), 29.35 (*C*H2), 29.01 (*C*H2), 19.88 (*C*H3). HR-MS (ESI) m/z: Calcd for C18H25O4: [M1 - H]- = 305.1758, found 305.1749.

3,4-dihydroxyphenethyl 3,5,5-trimethylhexanoate (**19**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / CH2Cl2 (1/2) as the eluent, affording the corresponding ester **19** in95% yield.

1H NMR (600 MHz, CDCl3) δ (ppm): 6.78 (d, *J* = 8.0 Hz, 1H, H-5’), 6.73 (d, *J* = 2.0 Hz, 1H, H-2’), 6.61 (dd, *J* = 8.0, 2.0 Hz, 1H, H-6’), 6.22 (br s, 1H, D2O exchang., 4’-O*H*), 6.13 (br s, 1H, D2O exchang., 3’-O*H*), 4.22 (t, *J* = 7.1 Hz, 2H, CH2C*H*2O), 2.80 (t, *J* = 7.1 Hz, 2H, C*H*2CH2O ), 2.29 (m, 1H, C*H*), 2.10 (m, 1H, C*H*), 2.03 – 1.95 (m, 1H, C*H*), 1.20 (m, 1H, C*H*), 1.09 (m, 1H, C*H*), 0.93 (d, *J* = 6.6 Hz, 3H, CH3), 0.88 (s, 9H, C*H*3). 13C NMR (151 MHz, CDCl3) δ (ppm): 173.52 (*C*O), 143.78 (C-3’), 142.37 (C-4’), 130.95 (C-1’), 121.47 (C-6’), 116.08 (C-2’), 115.50 (C-5’), 64.99 (CH2*C*H2O), 50.68 (*C*H2CH), 44.21 (*C*H2CH), 34.65 (*C*H2CH2O), 31.19 (C), 30.07 (3 x C*H*3), 27.17 (*C*H), 22.78 (C*H*3). HR-MS (ESI) m/z: Calcd for C17H25O4: [M1 - H]- = 293.1758, found 293.1750.

3,4-dihydroxyphenethyl 2-cyclohexylacetate (**20**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (4/1) as the eluent, affording the corresponding ester **20** in95% yield, as an oil.

1H NMR (400 MHz, CDCl3) δ (ppm): 6.81 (d, *J* = 8.0 Hz, 1H, H-5’), 6.75 (d, *J* = 1.8 Hz, 1H, H-2’), 6.62 (dd, *J* = 8.0, 1.8 Hz, 1H, H-6’), 4.27 (t, *J* = 7.0 Hz, 2H, CH2C*H*2O), 2.84 (t, *J* = 7.0 Hz, 2H, C*H*2CH2O), 2.19 (d, *J* = 7.1 Hz, 2H, COC*H*2), 1.82–1.60 (m, 6H, H-1, H-2, H-3, H-4, H-5, H-6), 1.31–1.08 (m, 3H, H-3, H-4, H-5), 0.98–0.91 (m, 2H, H-2, H-6). 13C NMR (151 MHz, CDCl3) δ (ppm):174.33 (*C*O), 143.89 (C-3’), 142.58 (C-4’), 130.18 (C-1’), 121.07 (C-6’), 115.83 (C-2’), 115.31 (C-5’), 65.23(CH2*C*H2O), 42.29 (CO*C*H2), 34.89 (*C*H2CH2O), 34.41 (C-1), 32.94 (C-2, C-6), 26.90 (C-4), 26.06 (C-3, C-5). HR-MS (ESI) m/z: Calcd for C16H21O4: [M1 - H]- = 277.1445, found 277.1436.

**General Procedure for the synthesis of compounds 21-24**

A solution of the appropriate ester (**2**, **3**, **4** or **11**) (1 mmol) in t-butanol (20 ml) was hydrogenated in the presence of 10% Pd/C (50 mg), under a pressure of 50 psi at room temperature for 3-4 h. After completion of the reaction, the resulting mixture was filtered through a celite pad and the filtrate was evaporated to dryness to afford the title compounds **21**-**24**.

2-(3,4-dihydroxyphenyl)-2-hydroxyethyl adamantane-1-carboxylate (**21**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (2/1) as the eluent, affording the corresponding ester **21** in81% yield.

Mp: 148-149 °C (CHCl3/*n*-pentane). 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 8.80 (br s, 1H, D2O exchang., 3’-O*H*), 8.73 (br s, 1H, D2O exchang., 4’-O*H*), 6.76 (d, *J* = 1.9 Hz, 1H, H-2’), 6.67 (d, *J* = 8.0 Hz, 1H, Η-5’), 6.59 (dd, *J* = 8.0, 1.9 Hz, 1H, Η-6’), 5.30 (d, *J* = 4.4 Hz, 1H, CHO*H*), 4.58-4.53 (m, 1H, C*H*CH2), 4.00–3.90 (m, 2H, CHC*H*2), 1.98-1.94 (m, 3H, C*H* adamantyl), 1.81-1.75 (m, 6H, C*H*2 adamantyl), 1.71-1.61 (m, 6H, C*H*2 adamantyl). 13C NMR (151 MHz, DMSO-*d6*) δ (ppm): 176.32 (*C*O), 144.87 (C-3’), 144.42 (C-4’), 133.14 (C-1’), 117.15 (C-6’), 115.02 (C-2’), 113.74 (C-5’), 70.08 (HO*C*HCH2), 68.41 (HOCH*C*H2), 40.05 (C adamantyl), 38.30 (*C*H2 adamantyl), 35.93 (*C*H2 adamantyl), 27.28 (*C*H adamantyl). HR-MS (ESI) m/z: Calcd for C19H23O5: [M1 - H]- = 331.1551, found 331.1545.

2-(3,4-dihydroxyphenyl)-2-hydroxyethyl 3,5-dihydroxybenzoate (**22**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (1/1) as the eluent, affording the corresponding ester **22** in76% yield.

Mp: 181-182 °C (CH2Cl2). 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 9.64 (br s, 2H, D2O exchang., 3-O*H*, 5-O*H*), 8.87 (br s, 1H, D2O exchang., 3’-O*H*), 8.82 (br s, 1H, D2O exchang., 4’-O*H*), 6.83 (s, 2H, H-2, H-6), 6.81 (s, 1H, H-2’), 6.69 (d, *J* = 8.0 Hz, 1H, Η-5’), 6.65 (d, *J* = 8.0 Hz, 1H, Η-6’), 6.44 (s, 1H, H-4), 5.47 (m, 1H, CHO*H*), 4.75-4.65 (m, 1H, C*H*CH2), 4.20-4.10 (m, 2H, CHC*H*2). 13C NMR (151 MHz, DMSO-*d6*) δ (ppm): 166.00 (*C*O), 158.46 (C-3,5), 145.00 (C-3’), 144.67 (C-4’), 132.82 (C-1’), 131.30 (C-1), 116.99 (C-6’), 115.04 (C-2’), 113.41 (C-5’), 107.26 (C-2, C-4, C-6), 69.93 (*C*HCH2), 69.23 (CH*C*H2). HR-MS (ESI) m/z: Calcd for C15H13O7: [M1 - H]- = 305.0667, found 305.0654.

2-(3,4-dihydroxyphenyl)-2-hydroxyethyl octanoate (**23**)

The crude product was purified by column chromatography (silica gel) using a mixture of cyclohexane / ethyl acetate (2/1) as the eluent, affording the corresponding ester **23** in87% yield.

Mp: 119-120 °C (CH2Cl2/*n*-pentane). 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 8.84 (br s, 1H, D2O exchang., 3’-O*H*), 8.77 (br s, 1H, D2O exchang., 4’-O*H*), 6.75 (d, *J* = 2.0 Hz, 1H, H-2’), 6.66 (d, *J* = 8.0 Hz, 1H, Η-5’), 6.57 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H, Η-6’), 5.34 (m, 1H, CHO*H*), 4.61-4.52 (m, 1H, C*H*CH2), 4.00–3.90 (m, 2H, CHC*H*2), 2.26 (t, *J* = 7.3 Hz, 2H, 2-C*H*2), 1.56-1.44 (m, 2H, 3-C*H*2), 1.34-1.14 (m, 8H, 4-C*H*2, 5-C*H*2, 6-C*H*2, 7-C*H*2), 0.85 (t, *J* = 7.3 Hz, 3H, C*H*3). 13C NMR (151 MHz, DMSO-*d6*) δ (ppm): 172.82 (*C*O), 144.93 (C-3’), 144.51 (C-4’), 132.97 (C-1’), 117.09 (C-6’), 115.10 (C-2’), 113.68 (C-5’), 69.83 (HO*C*HCH2), 68.79 (HOCH*C*H2), 33.37 (C-2), 31.09 (C-6), 28.36 (C-4, C-5), 24.41 (C-3), 22.03 (C-7), 13.93 (C-8). HR-MS (ESI) m/z: Calcd for C16H23O5: [M1 - H]- = 295.1550, found 295.1543.

2-(3,4-dihydroxyphenyl)-2-hydroxyethyl 3,5,5-trimethylhexanoate (**24**)

The crude product was purified by column chromatography (silica gel) using a mixture of CH2Cl2 / MeOH (100/1) as the eluent, affording the corresponding ester **24** in94% yield, as an oil.

1H NMR (600 MHz, Acetone-*d6*) δ (ppm): 7.08 (br s, 1H, D2O exchang., O*H*), 6.92 (d, *J* = 1.9 Hz, 1H, H-2’), 6.78 (d, *J* = 8.0 Hz, 1H, Η-5’), 6.74 (dd, *J* = 8.0, 1.9 Hz, 1H, Η-6’), 4.76 (m, 1H, CHO*H*), 4.15-4.03 (m, 2H, C*H*CH2), 2.29 (m, 1H, C*H*), 2.15-2.07 (m, 2H, 2 x C*H*), 1.28 (m, 1H, C*H*), 1.10 (m, 1H, C*H*), 0.95 (d, *J* = 6.6 Hz, 3H, CH3), 0.91 (s, 9H, C*H*3). 13C NMR (151 MHz, Acetone-*d6*) δ (ppm): 172.11 (*C*O), 144.85 (C-3’), 144.47 (C-4’), 133.64 (C-1’), 117.75 (C-6’), 114.85 (C-2’), 113.39 (C-5’), 71.12 (HO*C*HCH2), 68.91 (HOCH*C*H2), 50.27 (*C*H2CH), 43.47 (*C*H2CH), 30.62 (C), 29.34 (3 x C*H*3), 26.75 (*C*H), 22.07 (C*H*3). HR-MS (ESI) m/z: Calcd for C17H25O5: [M1 - H]- = 309.1707, found 309.1696.

**Supplementary figures**

**Supplementary Figure 1**. Synthesized analogs of HT

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**Supplementary Figure 2.** Overnight growth of *C. albicans* in the presence of HT analogs. Control stands for a culture where instead of an HT analog, DMSO solvent was added in a concentration identical to that in which HT analogs were dissolved. Growth is recorded after 24 h as O.D. values at 600 nm.

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**Supplementary Figure 3.** Comparison of antifungal activity of HT, amphotericin B and selected HT analogs. The concentration of antifungals shown is 100 μΜ. Control stands for a culture where DMSO solvent was added in a concentration identical to that of antifungals.

**Supplementary Figure 4. Antibacterial activity of HT analogs against *P. aeruginosa* and *P. fluorescens.*** Growth curves on the left showO.D. values recorded hourly at 600 nm. Column bar graphs on the right show the growth after 24 hours after the HT analogs addition, at 600 nm. Control stands for a culture DMSO solvent was added in a concentration identical to that of HT analogs.

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**Supplementary Figure 5. Epifluorescence *in vivo* microscopy showing the apparent non-effect of HT analogs 2 and 11 (37.5 μΜ) on *A. nidulans* cell wall**.The picture shows hyphae of strains expressingfunctional, GFP-tagged,FurA as PM molecular marker, stained with Calcuofluor white as a standard marker for cell wall integrity (Martzoukou et al., 2017).