Subtle side-chain modifications of the hop phytoestrogen 8-prenyl-naringenin result in distinct agonist/antagonist activity profiles for estrogen receptors α and β

Frederik Roelens, Nina Heldring, Willem Dhooge, Martin Bengtsson, Frank Comhaire, Jan-Åke Gustafsson, Eckardt Treuter, and Denis De Keukeleire

Chemical compounds and synthetic procedures

General Information

^{1}H NMR and ^{13}C NMR spectra were obtained with a Varian Mercury 300 spectrometer (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz). All spectra were recorded in DMSO-d_6. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the residual solvent peak. All signals assigned to hydroxyl groups were exchangeable with D_2O. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, n = nonet, m = multiplet, dd = double doublet, br = broad. Combustion analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. Exact mass measurements were performed on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Q-TOF 1, Micromass, Manchester, UK) equipped with a standard electrospray ionization (ESI) interface. Samples were infused in acetonitrile (positive mode: 1% formic acid) at 10 µL/min. Thin layer chromatography was carried out on precoated Alugram SIL G/UV$_{254}$ silica gel plates (Macherey-Nagel, Düren, Germany) and TLC separations were examined under UV light at 254 nm and revealed by a sulfuric acid - anisaldehyde spray. Column chromatography was carried out on silica (Ecochrom, ICN Silica 63-200 mesh) from ICN Biomedicals (Eschwege, Germany). Compounds were obtained as amorphous powders or as oils. Technical solvents were purchased from Chemlab (Zedelgem, Belgium), while anhydrous solvents and reagents were obtained from Acros Organics (Geel, Belgium) and Sigma-Aldrich (Bornem, Belgium). All reactions were performed under a nitrogen atmosphere. For the sake of uniformity, the nature of the alkyl group precedes other substituents in the naming of the compounds (deviation from the alphabetical ordening according to IUPAC nomenclature). Reference compounds E2, naringenin, and genistein were acquired from Sigma-Aldrich. 8-PN was synthesized according to a literature procedure.[1]

General procedure for the preparation of 8-alkylnaringenins

1. General procedure for the preparation of 2-alkyl-1,3,5-trimethoxybenzenes (**2a-j**)
1.1. General procedure for the preparation of 2-alkyl-1,3,5-trimethoxybenzenes (**2b-j**)

(i) To a stirring solution of 2,4,6-trimethoxybenzaldehyde (**1**) in dry Et_2O (1.5 mL/mmol) was added dropwise at -78 °C alkyllithium or alkylmagnesium bromide (1.2 equiv). The cooling bath was removed and, after completion of the reaction (1 - 1.5 h, as monitored by TLC), the reaction mixture was poured on ice and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. (ii) Without purification, the residue was redissolved in dry CH_2Cl_2 (1.5 mL/mmol) and $HSiEt_3$ (2.0 equiv) was added at room temperature together with CF_3COOH (6 equiv) at -78 °C.[2] The reaction mixture was allowed to warm to room temperature (1 h) and stirred until completion of the reaction (30 min - 1 h, as monitored by TLC). After neutralization with saturated aqueous $NaHCO_3$, the mixture was extracted with Et_2O. The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc) to yield **2b-j**.

1.2. Procedure for the preparation of 2-methyl-1,3,5-trimethoxybenzene (**2a**)

(i) 2,4,6-Trimethoxybenzyl alcohol was synthesized from **1** according to a literature procedure.[3] (ii) See general method for preparation of **2b-j** (1.1.(ii)).

2-Methyl-1,3,5-trimethoxybenzene (2a). Yield: 98%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.93 (s, 3H), 3.74 (s, 9H), 6.17 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 8.19, 55.47, 55.83, 90.91, 105.51, 158.93, 159.49. HRMS calcd for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1021; found 183.1033.

2-*n*-Propyl-1,3,5-trimethoxybenzene (2b). Yield: 99%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 (br t, 3H, J = 7.3 Hz), 1.35 (m, 2H), 2.41 (br t, 2H, J = 7.3 Hz), 3.71 (s, 6H), 3.72 (s, 3H), 6.17 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.65, 22.98, 24.84, 55.73, 56.18, 91.37, 110.70, 159.00, 159.60. HRMS calcd for $C_{12}H_{19}O_3$ $[M + H]^+$ 211.1334; found 211.1326.

2-*n*-Pentyl-1,3,5-trimethoxybenzene (2c). Yield: 96%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, J = 7.0 Hz), 1.15-1.40 (m, 6H), 2.43 (br t, 2H, J = 7.0 Hz), 3.71 (s, 6H), 3.72 (s, 3H), 6.16 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.59, 22.66, 22.71, 29.50, 31.97, 55.69, 56.14, 91.26, 110.85, 158.90, 159.53. HRMS calcd for $C_{14}H_{23}O_3$ $[M + H]^+$ 239.1647; found 239.1662.

2-*n*-Heptyl-1,3,5-trimethoxybenzene (2d). Yield: 99%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 7.0 Hz), 1.18-1.41 (m, 10H), 2.44 (br t, 2H, J = 7.3 Hz), 3.71 (s, 6H), 3.72 (s, 3H), 6.16 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.52, 22.66, 22.84, 29.35, 29.75, 29.82, 32.07, 55.60, 56.02, 91.22, 110.98, 158.93, 159.55. HRMS calcd for $C_{16}H_{27}O_3$ $[M + H]^+$ 267.1960; found 267.1944.

2-*n*-Nonyl-1,3,5-trimethoxybenzene (2e). Yield: 97%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 7.0 Hz), 1.15-1.39 (m, 14H), 2.42 (br t, 2H, J = 7.0 Hz), 3.71 (s, 6H), 3.72 (s, 3H), 6.16 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.59, 22.67, 22.78, 29.42, 29.62, 29.68, 29.71, 29.77, 32.00, 55.72, 56.17, 91.33, 110.90, 158.92, 159.54. HRMS calcd for $C_{18}H_{31}O_3$ $[M + H]^+$ 295.2273; found 295.2267.

2-*n*-Undecyl-1,3,5-trimethoxybenzene (2f). Yield: 93%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 7.0 Hz), 1.15-1.42 (m, 18H), 2.42 (br t, 2H, J = 6.7 Hz), 3.69 (s, 6H), 3.71 (s, 3H), 6.14 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.50, 22.66, 22.83, 29.50, 29.70, 29.80, 32.05, 55.59, 55.98, 91.14, 110.89, 158.87, 159.51. HRMS calcd for $C_{20}H_{35}O_3$ $[M + H]^+$ 323.2586; found 323.2569.

2-(3-Methylbutyl)-1,3,5-trimethoxybenzene (2g). Yield: 98%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.86 (br d, 6H, J = 6.7 Hz), 1.21 (br q, 2H, J = 7.0 Hz), 1.44 (br n, 1H, J = 6.7 Hz), 2.44 (br t, 2H, J = 6.7 Hz), 3.71 (s, 6H), 3.72 (s, 3H), 6.16 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 20.74, 23.18, 28.23, 39.19, 55.70, 56.18, 91.29, 111.02, 158.85, 159.51. HRMS calcd for $C_{14}H_{23}O_3$ $[M + H]^+$ 239.1647; found 239.1663.

2-(2-Methylpropyl)-1,3,5-trimethoxybenzene (2h). Yield: 99%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.78 (br d, 6H, J = 6.7 Hz), 1.74 (br n, 1H, J = 6.7 Hz), 2.34 (br d, 2H, J = 7.0 Hz), 3.71 (s, 6H), 3.74 (s, 3H), 6.18 (s, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 23.05, 28.63, 31.71, 55.67, 56.09, 91.20, 109.86, 159.21, 159.59. HRMS calcd for $C_{13}H_{21}O_3$ $[M + H]^+$ 225.1491; found 225.1501.

2-(2,2-Dimethylpropyl)-1,3,5-trimethoxybenzene (2i). Yield: 99%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 2.41 (s, 2H), 3.68 (s, 6H), 3.74 (s, 3H), 6.18 (s, 2H);

^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.44, 33.56, 35.32, 55.68, 55.86, 91.19, 108.46, 159.67, 159.71. HRMS calcd for $C_{14}H_{23}O_3$ $[M + H]^+$ 239.1647; found 239.1631.
2-Benzyl-1,3,5-trimethoxybenzene (2j). Yield: 97%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.73 (s, 6H), 3.75 (s, 3H), 3.80 (s, 2H), 6.23 (s, 2H), 7.04-7.21 (m, 5H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.52, 55.84, 56.31, 91.51, 109.46, 125.92, 128.59, 128.74, 142.39, 159.01, 160.21. HRMS calcd for $C_{16}H_{19}O_3$ $[M + H]^+$ 259.1334; found 259.1352.

2. General procedure for the preparation of 3-alkyl-2,4,6-trimethoxy-acetophenones (**3a-j**)
To a stirring solution of 2-alkyl-1,3,5-trimethoxybenzene (**2a-j**) in dry CH_2Cl_2 (1 mL/mmol) was added dropwise at -10 °C $SnCl_4$ (2 equiv) and acetyl chloride (1.5 equiv). The reaction mixture was stirred until completion of the reaction (2 - 3 h, as monitored by TLC), and poured on ice. The separated aqueous phase was extracted with Et_2O, and both organic phases were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc) to yield **3a-j**.

3-Methyl-2,4,6-trimethoxyacetophenone (3a). Yield: 77%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.36 (s, 3H), 3.59, 3.80 and 3.83 (3s, 3H each s), 6.49 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 8.87, 33.03, 56.41, 56.54, 62.49, 92.60, 111.31, 118.52, 155.92, 156.19, 160.14, 201.47. HRMS calcd for $C_{12}H_{17}O_4$ $[M + H]^+$ 225.1127; found 225.1124.
3-*n*-Propyl-2,4,6-trimethoxyacetophenone (3b). Yield: 86%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.87 (br t, 3H, J = 7.3 Hz), 1.43 (m, 2H), 2.36 (s, 3H), 2.41 (br t, 2H, J = 7.3 Hz), 3.59, 3.79 and 3.82 (3s, 3H each s), 6.48 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.85, 23.34, 25.62, 33.04, 56.49, 56.57, 63.28, 92.90, 116.33, 118.45, 156.21, 156.38, 160.27, 201.61. HRMS calcd for $C_{14}H_{21}O_4$ $[M + H]^+$ 253.1440; found 253.1435.
3-*n*-Pentyl-2,4,6-trimethoxyacetophenone (3c). Yield: 84%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.84 (br t, 3H, J = 6.8 Hz), 1.21-1.45 (m, 6H), 2.36 (s, 3H), 2.42 (br t, 2H, J = 7.3 Hz), 3.58, 3.78 and 3.81 (3s, 3H each s), 6.47 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.50, 22.60, 23.41, 29.79, 32.20, 33.00, 56.43, 56.49, 63.26, 92.77, 116.49, 118.40, 156.15, 156.27, 160.19, 201.61. HRMS calcd for $C_{16}H_{25}O_4$ $[M + H]^+$ 281.1753; found 281.1747.
3-*n*-Heptyl-2,4,6-trimethoxyacetophenone (3d). Yield: 90%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.84 (br t, 3H, J = 7.0 Hz), 1.18-1.44 (m, 10H), 2.36 (s, 3H), 2.42 (br t, 2H, J = 7.3 Hz), 3.58, 3.78 and 3.81 (3s, 3H each s), 6.47 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.62, 22.77, 23.46, 29.13, 29.90, 30.07, 31.92, 33.08, 56.55, 56.63, 63.29, 92.98, 116.57, 118.49, 156.17, 156.31, 160.21, 201.61. HRMS calcd for $C_{18}H_{29}O_4$ $[M + H]^+$ 309.2066; found 309.2054.
3-*n*-Nonyl-2,4,6-trimethoxyacetophenone (3e). Yield: 94%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 6.7 Hz), 1.16-1.44 (m, 14H), 2.36 (s, 3H), 2.42 (br t, 2H, J = 7.0 Hz), 3.58, 3.78 and 3.81 (3s, 3H each s), 6.47 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.58, 22.77, 23.46, 29.39, 29.49, 29.63, 29.94, 30.06, 31.99, 33.06, 56.51, 56.58, 63.29, 92.90, 116.52, 118.45, 156.15, 156.29, 160.19, 201.60. HRMS calcd for $C_{20}H_{33}O_4$ $[M + H]^+$ 337.2379; found 337.2393.

3-*n*-Undecyl-2,4,6-trimethoxyacetophenone (3f). Yield: 91%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 (br t, 3H, J = 6.7 Hz), 1.22-1.45 (m, 18H), 2.34 (s, 3H), 2.41 (br t, 2H, J = 7.0 Hz), 3.57, 3.77 and 3.79 (3s, 3H each s), 6.46 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.53, 22.81, 23.45, 29.47, 29.55, 29.74, 29.77, 29.80, 30.00, 30.09, 32.03, 32.97, 56.39, 56.49, 63.22, 92.75, 116.47, 118.39, 156.13, 156.26, 160.16, 201.51. HRMS calcd for $C_{22}H_{37}O_4$ $[M + H]^+$ 365.2692; found 365.2687.
3-(3-Methylbutyl)-2,4,6-trimethoxyacetophenone (3g). Yield: 96%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.88 (br d, 6H, J = 6.5 Hz), 1.28 (br q, 2H, J = 6.7 Hz), 1.51 (br n, 1H, J = 6.7 Hz), 2.36 (s, 3H), 2.42 (br t, 2H, J = 7.0 Hz), 3.59, 3.78 and 3.81 (3s, 3H each s), 6.47 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 21.44, 23.08, 28.51, 33.11, 39.40, 56.56, 56.59, 63.34, 92.92, 116.68, 118.48, 156.11, 156.20, 160.15, 201.69. HRMS calcd for $C_{16}H_{25}O_4$ $[M + H]^+$ 281.1753; found 281.1742.
3-(2-Methylpropyl)-2,4,6-trimethoxyacetophenone (3h). Yield: 95%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 (br d, 6H, J = 6.7 Hz), 1.79 (br n, 1H, J = 6.7 Hz), 2.35 (br d, 2H, J = 7.3 Hz), 2.38 (s, 3H), 3.57, 3.80 and 3.81 (3s, 3H each s), 6.49 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 23.15, 28.80, 32.29, 33.11, 56.46, 56.54, 62.97, 92.70, 115.27, 118.16, 156.23, 156.80, 160.34, 201.74. HRMS calcd for $C_{15}H_{23}O_4$ $[M + H]^+$ 267.1596; found 267.1582.
3-(2,2-Dimethylpropyl)-2,4,6-trimethoxyacetophenone (3i). Yield: 98%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (s, 9H), 2.37 (s, 3H), 2.41 (s, 2H), 3.52, 3.77 and 3.79 (3s, 3H each s), 6.47 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.39, 33.10, 33.69, 35.86, 56.15, 56.49, 62.54, 92.51, 113.60, 118.13, 156.28, 157.47, 160.73, 201.73. HRMS calcd for $C_{16}H_{25}O_4$ $[M + H]^+$ 281.1753; found 281.1742.
3-Benzyl-2,4,6-trimethoxyacetophenone (3j). Yield: 94%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H), 3.50, 3.80 and 3.81 (3s, 3H each s), 3.82 (s, 2H), 6.54 (s, 1H), 7.06-7.24 (m, 5H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.97, 33.10, 56.69, 63.17, 93.07, 114.81, 118.51, 126.21, 128.64, 128.76, 141.76, 156.62, 156.88, 160.22, 201.52. HRMS calcd for $C_{18}H_{21}O_4$ $[M + H]^+$ 301.1440; found 301.1432.

3. General procedure for the preparation of 3-alkyl-2,4,6-trihydroxy-acetophenones (**4a-j**)
To a stirring solution of 3-alkyl-2,4,6-trimethoxyacetophenone (**3a-j**) in dry CH_2Cl_2 (2 mL/mmol) BBr_3 (4 equiv, 1.0 M in CH_2Cl_2) was added dropwise at -78 °C. The mixture was allowed to warm to room temperature and was stirred until completion of the reaction (24 - 48 h, as monitored by TLC). After cooling to 0 °C, the reaction was quenched by pouring on ice. The organic solvent was removed under reduced pressure and the aqueous suspension was repeatedly extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (hexane/EtOAc) to provide **4a-j**.

3-Methyl-2,4,6-trihydroxyacetophenone (4a). Yield: 80%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.81 (s, 3H), 2.53 (s, 3H), 5.98 (s, 1H), 10.29, 10.52 and 13.95 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 7.98, 33.16, 94.52, 101.92, 104.42, 160.69, 163.32, 164.00, 203.10. HRMS calcd for $C_9H_9O_4$ $[M - H]^-$ 181.0501; found 181.0512.
3-*n*-Propyl-2,4,6-trihydroxyacetophenone (4b). Yield: 77%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 7.3 Hz), 1.37 (m, 2H), 2.35 (br t, 2H, J = 7.3 Hz), 2.52 (s, 3H), 5.97 (s, 1H), 10.21, 10.50 and 13.97 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-

d_6) δ 14.74, 22.47, 24.44, 33.18, 94.56, 104.41, 106.97, 160.78, 163.37, 164.12, 203.15. HRMS calcd for $C_{11}H_{13}O_4$ $[M - H]^-$ 209.0814; found 209.0811.

3-*n*-Pentyl-2,4,6-trihydroxyacetophenone (4c). Yield: 70%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, J = 6.6 Hz), 1.15-1.43 (m, 6H), 2.36 (br t, 2H, J = 7.7 Hz), 2.52 (s, 3H), 5.96 (s, 1H), 10.19, 10.48 and 13.97 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.67, 22.31, 22.76, 28.96, 32.02, 33.17, 94.57, 104.42, 107.20, 160.74, 163.30, 164.06, 203.14. HRMS calcd for $C_{13}H_{17}O_4$ $[M - H]^-$ 237.1127; found 237.1125.

3-*n*-Heptyl-2,4,6-trihydroxyacetophenone (4d). Yield: 82%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, J = 6.6 Hz), 1.15-1.40 (m, 10H), 2.37 (br t, 2H, J = 7.7 Hz), 2.52 (s, 3H), 5.97 (s, 1H), 10.15, 10.45 and 13.95 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.62, 22.35, 22.79, 29.30, 29.36, 29.78, 32.03, 33.12, 94.59, 104.45, 107.24, 160.72, 163.30, 164.07, 203.10. HRMS calcd for $C_{15}H_{21}O_4$ $[M - H]^-$ 265.1440; found 265.1430.

3-*n*-Nonyl-2,4,6-trihydroxyacetophenone (4e). Yield: 69%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 7.0 Hz), 1.15-1.42 (m, 14H), 2.36 (br t, 2H, J = 7.0 Hz), 2.52 (s, 3H), 5.96 (s, 1H), 10.16, 10.45 and 13.95 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.62, 22.35, 22.77, 29.26, 29.39, 29.69, 29.78, 29.85, 31.97, 33.13, 94.59, 104.45, 107.23, 160.72, 163.30, 164.06, 203.11. HRMS calcd for $C_{17}H_{25}O_4$ $[M - H]^-$ 293.1753; found 293.1743.

3-*n*-Undecyl-2,4,6-trihydroxyacetophenone (4f). Yield: 53%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, J = 7.0 Hz), 1.14-1.44 (m, 18H), 2.35 (br t, 2H, J = 7.0 Hz), 2.52 (s, 3H), 5.96 (s, 1H), 10.18, 10.48 and 13.97 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.65, 22.35, 22.80, 29.27, 29.41, 29.69, 29.71, 29.75, 29.80, 31.99, 33.18, 94.55, 104.40, 107.19, 160.73, 163.30, 164.06, 203.12. HRMS calcd for $C_{19}H_{29}O_4$ $[M - H]^-$ 321.2066; found 321.2049.

3-(3-Methylbutyl)-2,4,6-trihydroxyacetophenone (4g). Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.86 (br d, 6H, J = 6.6 Hz), 1.23 (br q, 2H, J = 6.6 Hz), 1.46 (br n, 1H, J = 6.6 Hz), 2.37 (br t, 2H, J = 7.6 Hz), 2.52 (s, 3H), 5.96 (s, 1H), 10.20, 10.48 and 13.99 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 20.38, 23.27, 28.30, 33.17, 38.56, 94.57, 104.57, 107.35, 160.72, 163.25, 164.01, 203.16. HRMS calcd for $C_{13}H_{17}O_4$ $[M - H]^-$ 237.1127; found 237.1124.

3-(2-Methylpropyl)-2,4,6-trihydroxyacetophenone (4h). Yield: 83%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br d, 6H, J = 6.6 Hz), 1.81 (br n, 1H, J = 6.6 Hz), 2.27 (br d, 2H, J = 7.6 Hz), 2.52 (s, 3H), 5.97 (s, 1H), 10.18, 10.50 and 14.00 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 23.17, 28.26, 31.39, 33.20, 94.53, 104.37, 107.63, 160.76, 163.62, 164.40, 203.14. HRMS calcd for $C_{12}H_{15}O_4$ $[M - H]^-$ 223.0970; found 223.0979.

3-(2,2-Dimethylpropyl)-2,4,6-trihydroxyacetophenone (4i). Yield: 86%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.84 (s, 9H), 2.35 (s, 2H), 2.53 (s, 3H), 5.98 (s, 1H), 10.13, 10.47 and 14.09 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.69, 33.16, 34.00, 35.09, 94.53, 104.34, 105.06, 160.85, 164.22, 165.16, 203.02. HRMS calcd for $C_{13}H_{17}O_4$ $[M - H]^-$ 237.1127; found 237.1123.

3-Benzyl-2,4,6-trihydroxyacetophenone (4j). Yield: 66%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.54 (s, 3H), 3.72 (s, 2H), 6.02 (s, 1H), 7.04-7.21 (m, 5H), 10.38, 10.58 and 14.08 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.10, 33.09, 94.72, 104.54, 106.20,

125.94, 128.56, 128.86, 142.36, 161.29, 163.32, 164.17, 203.27. HRMS calcd for $C_{15}H_{13}O_4$ [M - H]$^-$ 257.0814; found 257.0826.

4. General procedure for the preparation of 3-alkyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenones (**5a-j**)

To a stirring mixture of 3-alkyl-2,4,6-trihydroxyacetophenone (**4a-j**) and anhydrous K_2CO_3 (7 equiv) in dry acetone (3 mL/mmol **4a-j**), MOMCl (2.5 equiv) was added dropwise.[4] The reaction mixture was heated to reflux and allowed to stir for 1 h. After cooling to room temperature, the reaction mixture was filtered and the organic phase was concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc), to afford **5a-j**.

3-Methyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5a). Yield: 64%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.93 (s, 3H), 2.61 (s, 3H), 3.37 and 3.42 (2s, 3H each s), 5.28 and 5.29 (2s, 2H each s), 6.37 (s, 1H), 13.82 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 8.11, 33.66, 56.72, 57.19, 92.37, 94.56, 95.21, 106.75, 106.87, 158.93, 161.41, 163.29, 204.24. HRMS calcd for $C_{13}H_{17}O_6$ [M - H]$^-$ 269.1025; found 269.1027.

3-*n*-Propyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5b). Yield: 68%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.86 (br t, 3H, *J* = 7.3 Hz), 1.42 (m, 2H), 2.49 (br t, 2H, *J* = 7.3 Hz), 2.61 (s, 3H), 3.37 and 3.43 (2s, 3H each s), 5.27 and 5.29 (2s, 2H each s), 6.34 (s, 1H), 13.84 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.72, 22.46, 24.56, 33.71, 56.74, 57.20, 92.10, 94.39, 95.17, 106.74, 111.35, 159.13, 161.42, 163.39, 204.30. HRMS calcd for $C_{15}H_{21}O_6$ [M - H]$^-$ 297.1338; found 297.1346.

3-*n*-Pentyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5c). Yield: 76%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, *J* = 6.6 Hz), 1.17-1.50 (m, 6H), 2.48 (br t, 2H, *J* = 7.7 Hz), 2.61 (s, 3H), 3.38 and 3.43 (2s, 3H each s), 5.27 and 5.29 (2s, 2H each s), 6.34 (s, 1H), 13.83 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.59, 22.44, 22.69, 28.89, 31.97, 33.71, 56.73, 57.20, 92.08, 94.38, 95.17, 106.73, 111.59, 159.10, 161.35, 163.34, 204.31. HRMS calcd for $C_{17}H_{25}O_6$ [M - H]$^-$ 325.1651; found 325.1668.

3-*n*-Heptyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5d). Yield: 66%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, *J* = 7.0 Hz), 1.17-1.45 (m, 10H), 2.48 (br t, 2H, *J* = 7.7 Hz), 2.61 (s, 3H), 3.38 and 3.43 (2s, 3H each s), 5.26 and 5.29 (2s, 2H each s), 6.34 (s, 1H), 13.81 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.62, 22.49, 22.77, 29.21, 29.26, 29.73, 31.94, 33.65, 56.71, 57.18, 92.14, 94.44, 95.21, 106.79, 111.67, 159.09, 161.35, 163.34, 204.25. HRMS calcd for $C_{19}H_{29}O_6$ [M - H]$^-$ 353.1964; found 353.1965.

3-*n*-Nonyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5e). Yield: 66%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, *J* = 7.0 Hz), 1.15-1.48 (m, 14H), 2.48 (br t, 2H, *J* = 7.7 Hz), 2.61 (s, 3H), 3.38 and 3.43 (2s, 3H each s), 5.26 and 5.29 (2s, 2H each s), 6.34 (s, 1H), 13.81 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.60, 22.48, 22.76, 29.17, 29.37, 29.59, 29.61, 29.73, 31.96, 33.65, 56.71, 57.18, 92.13, 94.44, 95.22, 106.79, 111.66, 159.09, 161.35, 163.34, 204.25. HRMS calcd for $C_{21}H_{33}O_6$ [M - H]$^-$ 381.2277; found 381.2271.

3-*n*-Undecyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5f). Yield: 73%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, *J* = 7.0 Hz), 1.14-1.46 (m, 18H), 2.47 (br t, 2H, *J* = 7.7 Hz), 2.60 (s, 3H), 3.37 and 3.42 (2s, 3H each s), 5.26 and 5.29 (2s, 2H each

s), 6.34 (s, 1H), 13.83 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.64, 22.48, 22.79, 29.18, 29.39, 29.58, 29.65, 29.69, 29.72, 31.97, 33.70, 56.71, 57.19, 92.07, 94.39, 95.17, 106.73, 111.59, 159.09, 161.34, 163.34, 204.27. HRMS calcd for $C_{23}H_{37}O_6$ [M - H]$^-$ 409.2590; found 409.2592.

3-(3-Methylbutyl)-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5g). Yield: 73%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.88 (br d, 6H, J = 6.6 Hz), 1.27 (br q, 2H, J = 6.7 Hz), 1.49 (br n, 1H, J = 6.6 Hz), 2.49 (br t, 2H, J = 7.6 Hz), 2.61 (s, 3H), 3.38 and 3.43 (2s, 3H each s), 5.27 and 5.29 (2s, 2H each s), 6.34 (s, 1H), 13.82 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 20.51, 23.17, 28.28, 33.63, 38.54, 56.75, 57.20, 92.24, 94.52, 95.26, 106.85, 111.89, 159.08, 161.29, 163.25, 204.28. HRMS calcd for $C_{17}H_{25}O_6$ [M - H]$^-$ 325.1651; found 325.1667.

3-(2-Methylpropyl)-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5h). Yield: 76%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br d, 6H, J = 6.6 Hz), 1.83 (br n, 1H, J = 6.6 Hz), 2.37 (br d, 2H, J = 7.3 Hz), 2.61 (s, 3H), 3.37 and 3.43 (2s, 3H each s), 5.26 and 5.30 (2s, 2H each s), 6.35 (s, 1H), 13.86 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 23.17, 28.33, 31.51, 33.73, 56.80, 57.23, 91.94, 94.45, 95.20, 106.65, 110.56, 159.21, 161.72, 163.68, 204.30. HRMS calcd for $C_{16}H_{23}O_6$ [M - H]$^-$ 311.1495; found 311.1488.

3-(2,2-Dimethylpropyl)-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5i). Yield: 78%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 9H), 2.46 (s, 2H), 2.62 (s, 3H), 3.38 and 3.44 (2s, 3H each s), 5.23 and 5.30 (2s, 2H each s), 6.37 (s, 1H), 13.94 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.67, 33.71, 33.88, 35.20, 56.97, 57.25, 91.89, 94.82, 95.24, 106.59, 109.25, 159.38, 162.54, 164.37, 204.25. HRMS calcd for $C_{17}H_{25}O_6$ [M - H]$^-$ 325.1651; found 325.1636.

3-Benzyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (5j). Yield: 81%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.62 (s, 3H), 3.26 and 3.43 (2s, 3H each s), 3.83 (s, 2H), 5.27 and 5.31 (2s, 2H each s), 6.38 (s, 1H), 7.04-7.22 (m, 5H), 13.93 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.24, 33.63, 56.73, 57.25, 92.20, 94.44, 95.30, 106.89, 110.43, 126.21, 128.70, 128.82, 141.57, 159.64, 161.36, 163.33, 204.35. HRMS calcd for $C_{19}H_{21}O_6$ [M - H]$^-$ 345.1338; found 345.1341.

5. General procedure for the preparation of 3'-alkyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcones (**6a-j**)

A solution of 3-alkyl-2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (**5a-j**) and *p*-methoxymethoxybenzaldehyde (1.1 equiv, synthesized from *p*-hydroxybenzaldehyde) in EtOH (2.5 mL/mmol **5a-j**) cooled to 5 °C, was added dropwise to a stirring mixture of KOH (0.7 g/mmol **5a-j**) in H_2O-EtOH (1.5 mL/mmol **5a-j**, 2:3 v/v) at 0 °C.[4] The reaction mixture was stirred at 0 °C for 3 h and then allowed to warm to room temperature and stirred for an additional 20 h (or until completion of the reaction, as monitored by TLC). The reaction mixture was then poured into ice water, the resulting solution was acidified with 1 M HCl to pH 4, and extracted with Et_2O. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc), to afford **6a-j**.

3'-Methyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6a). Yield: 74%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.96 (s, 3H), 3.37, 3.39 and 3.42 (3s, 3H each s), 5.24,

5.29 and 5.33 (3s, 2H each s), 6.42 (s, 1H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.67 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 15.8 Hz), 7.79 (d, 1H, *J* = 15.8 Hz), 13.60 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 8.31, 56.44, 56.74, 57.23, 93.30, 94.36, 94.62, 95.89, 107.27, 107.91, 117.22, 126.02, 129.04, 130.93, 143.14, 158.12, 159.43, 161.14, 163.10, 193.49. HRMS calcd for $C_{22}H_{25}O_8$ [M - H]$^-$ 417.1549; found 417.1535.

3'-*n*-Propyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6b). Yield: 83%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.87 (br t, 3H, *J* = 7.3 Hz), 1.45 (m, 2H), 2.48 (br t, 2H, *J* = 7.0 Hz), 3.36, 3.39 and 3.43 (3s, 3H each s), 5.24, 5.29 and 5.34 (3s, 2H each s), 6.40 (s, 1H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.67 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 15.8 Hz), 7.80 (d, 1H, *J* = 15.8 Hz), 13.66 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.76, 22.51, 24.74, 56.43, 56.76, 57.25, 92.99, 94.33, 94.44, 95.86, 107.70, 111.83, 117.21, 126.00, 129.05, 130.93, 143.03, 158.39, 159.41, 161.24, 163.29, 193.51. HRMS calcd for $C_{24}H_{29}O_8$ [M - H]$^-$ 445.1862; found 445.1876.

3'-*n*-Pentyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6c). Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.84 (br t, 3H, *J* = 6.6 Hz), 1.19-1.49 (m, 6H), 2.51 (br t, 2H, *J* = 7.0 Hz), 3.36, 3.39 and 3.43 (3s, 3H each s), 5.24, 5.29 and 5.34 (3s, 2H each s), 6.39 (s, 1H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.67 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 15.4 Hz), 7.80 (d, 1H, *J* = 15.4 Hz), 13.67 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.60, 22.71, 28.94, 32.00, 56.43, 56.76, 57.25, 92.99, 94.34, 94.44, 95.86, 107.69, 112.07, 117.20, 126.01, 129.06, 130.92, 143.01, 158.36, 159.41, 161.16, 163.25, 193.50. HRMS calcd for $C_{26}H_{33}O_8$ [M - H]$^-$ 473.2175; found 473.2189.

3'-*n*-Heptyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6d). Yield: 79%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.84 (br t, 3H, *J* = 7.0 Hz), 1.20-1.44 (m, 10H), 2.49 (br t, 2H, *J* = 7.0 Hz), 3.37, 3.39 and 3.43 (3s, 3H each s), 5.24, 5.28 and 5.34 (3s, 2H each s), 6.39 (s, 1H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.66 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 15.8 Hz), 7.81 (d, 1H, *J* = 15.8 Hz), 13.66 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.63, 22.67, 22.78, 29.28, 29.77, 31.95, 56.42, 56.74, 57.24, 93.04, 94.39, 94.50, 95.90, 107.74, 112.14, 117.22, 126.04, 129.09, 130.89, 142.98, 158.36, 159.42, 161.17, 163.27, 193.50. HRMS calcd for $C_{28}H_{37}O_8$ [M - H]$^-$ 501.2488; found 501.2471.

3'-*n*-Nonyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6e). Yield: 76%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, *J* = 6.6 Hz), 1.12-1.48 (m, 14H), 2.49 (br t, 2H, *J* = 7.0 Hz), 3.37, 3.39 and 3.43 (3s, 3H each s), 5.24, 5.29 and 5.34 (3s, 2H each s), 6.39 (s, 1H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.66 (d, 2H, *J* = 8.8 Hz), 7.71 (d, 1H, *J* = 15.8 Hz), 7.81 (d, 1H, *J* = 15.8 Hz), 13.67 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.64, 22.78, 29.23, 29.39, 29.58, 29.63, 29.78, 31.98, 56.43, 56.74, 57.25, 92.97, 94.33, 94.44, 95.86, 107.69, 112.06, 117.20, 126.00, 129.05, 130.92, 143.02, 158.36, 159.41, 161.16, 163.25, 193.50. HRMS calcd for $C_{30}H_{41}O_8$ [M - H]$^-$ 529.2801; found 529.2794.

3'-*n*-Undecyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6f). Yield: 92%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 (br t, 3H, *J* = 6.6 Hz), 1.14-1.48 (m, 18H), 2.50 (br t, 2H, *J* = 7.0 Hz), 3.36, 3.39 and 3.43 (3s, 3H each s), 5.24, 5.28 and 5.34 (3s, 2H each s), 6.39 (s, 1H), 7.08 (d, 2H, *J* = 8.8 Hz), 7.66 (d, 2H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 15.8 Hz), 7.81 (d, 1H, *J* = 15.8 Hz), 13.70 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.63, 22.65, 22.80, 29.22, 29.42, 29.62, 29.68, 29.71, 29.75, 31.99, 56.41, 56.71, 57.23, 92.94, 94.33, 94.44, 95.85, 107.65, 112.07, 117.19, 125.98, 129.06, 130.89, 142.98, 158.37, 159.40, 161.16, 163.33, 193.47. HRMS calcd for $C_{32}H_{45}O_8$ [M - H]$^-$ 557.3114; found 557.3115.

3'-(3-Methylbutyl)-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6g). Yield: 91%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.89 (br d, 6H, J = 6.5 Hz), 1.30 (br q, 2H, J = 7.3 Hz), 1.50 (br n, 1H, J = 6.5 Hz), 2.52 (br t, 2H, J = 7.6 Hz), 3.37, 3.40 and 3.43 (3s, 3H each s), 5.24, 5.29 and 5.34 (3s, 2H each s), 6.39 (s, 1H), 7.08 (d, 2H, J = 8.5 Hz), 7.67 (d, 2H, J = 8.5 Hz), 7.70 (d, 1H, J = 15.5 Hz), 7.80 (d, 1H, J = 15.5 Hz), 13.68 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 20.69, 23.21, 28.33, 38.57, 56.43, 56.78, 57.25, 93.00, 94.32, 94.47, 95.86, 107.68, 112.25, 117.21, 125.99, 129.05, 130.93, 143.00, 158.35, 159.40, 161.10, 163.20, 193.50. HRMS calcd for $C_{26}H_{33}O_8$ $[M - H]^-$ 473.2175; found 473.2196.

3'-(2-Methylpropyl)-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6h). Yield: 92%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.85 (br d, 6H, J = 6.6 Hz), 1.86 (br n, 1H, J = 6.6 Hz), 2.41 (br d, 2H, J = 7.3 Hz), 3.37, 3.39 and 3.43 (3s, 3H each s), 5.24, 5.28 and 5.35 (3s, 2H each s), 6.40 (s, 1H), 7.08 (d, 2H, J = 8.8 Hz), 7.67 (d, 2H, J = 8.8 Hz), 7.70 (d, 1H, J = 15.8 Hz), 7.81 (d, 1H, J = 15.8 Hz), 13.70 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 23.19, 28.37, 31.66, 56.43, 56.82, 57.28, 92.79, 94.33, 94.49, 95.87, 107.56, 110.99, 117.21, 126.03, 129.06, 130.93, 143.00, 158.48, 159.41, 161.55, 163.60, 193.51. HRMS calcd for $C_{25}H_{31}O_8$ $[M - H]^-$ 459.2019; found 459.2033.

3'-(2,2-Dimethylpropyl)-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6i). Yield: 91%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.89 (s, 9H), 2.49 (s, 2H), 3.37, 3.40 and 3.44 (3s, 3H each s), 5.24, 5.25 and 5.35 (3s, 2H each s), 6.41 (s, 1H), 7.08 (d, 2H, J = 8.8 Hz), 7.66 (d, 2H, J = 8.8 Hz), 7.69 (d, 1H, J = 15.4 Hz), 7.80 (d, 1H, J = 15.4 Hz), 13.78 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.67, 33.92, 35.34, 56.43, 56.99, 57.30, 92.72, 94.38, 94.86, 95.89, 107.47, 109.66, 117.23, 126.14, 129.11, 130.89, 142.88, 158.66, 159.41, 162.36, 164.31, 193.51. HRMS calcd for $C_{26}H_{33}O_8$ $[M - H]^-$ 473.2175; found 473.2188.

3'-Benzyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (6j). Yield: 93%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.26, 3.36 and 3.43 (3s, 3H each s), 3.86 (s, 2H), 5.24, 5.29 and 5.36 (3s, 2H each s), 6.43 (s, 1H), 7.04-7.69 (m, 9H), 7.72 (d, 1H, J = 15.8 Hz), 7.81 (d, 1H, J = 15.8 Hz), 13.81 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.38, 56.43, 56.75, 57.30, 92.95, 94.34, 95.89, 107.72, 110.78, 117.22, 125.90, 126.26, 128.75, 128.85, 129.02, 130.97, 141.57, 143.23, 158.90, 159.45, 161.16, 163.26, 193.51. HRMS calcd for $C_{28}H_{29}O_8$ $[M - H]^-$ 493.1862; found 493.1875.

6. General procedure for the preparation of 8-alkyl-5,7,4'-tris(methoxymethoxy)flavanones (**7a-j**)

To a stirring solution of 3'-alkyl-2'-hydroxy-4,4',6'-tris(methoxymethoxy)chalcone (**6a-j**) in EtOH (5 mL/mmol) were added NaOAc (4 equiv) and H_2O (0.4 mL/mmol **6a-j**).[4] The reaction mixture was heated to reflux for 20 h and allowed to cool to room temperature. The mixture was then diluted with H_2O and extracted with Et_2O. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc) to afford **7a-j**, while **6a-j** was recovered also.

8-Methyl-5,7,4'-tris(methoxymethoxy)flavanone (7a). Yield: 53%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.96 (s, 3H), 2.66 (dd, 1H, J = 2.9, 16.4 Hz), 3.03 (dd, 1H, J = 12.6, 16.4 Hz), 3.36, 3.37 and 3.38 (3s, 3H each s), 5.17, 5.19 and 5.27 (3s, 2H each s), 5.48

(dd, 1H, *J* = 2.9, 12.6 Hz), 6.49 (s, 1H), 7.05 (d, 2H, *J* = 8.5 Hz), 7.43 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 8.77, 45.33, 56.24, 56.70, 78.27, 94.42, 94.61, 95.78, 96.67, 107.75, 108.05, 116.78, 128.42, 133.02, 157.39, 157.56, 160.67, 161.35, 189.46. HRMS calcd for $C_{22}H_{27}O_8$ $[M + H]^+$ 419.1706; found 419.1691.

8-*n*-Propyl-5,7,4'-tris(methoxymethoxy)flavanone (7b). Yield: 61%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, *J* = 7.3 Hz), 1.45 (m, 2H), 2.50 (br t, 2H, *J* = 7.0 Hz), 2.66 (dd, 1H, *J* = 2.6, 16.5 Hz), 2.98 (dd, 1H, *J* = 12.5, 16.5 Hz), 3.36, 3.37 and 3.39 (3s, 3H each s), 5.17, 5.19 and 5.26 (3s, 2H each s), 5.45 (dd, 1H, *J* = 2.6, 12.5 Hz), 6.48 (s, 1H), 7.05 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.65, 22.70, 24.99, 45.60, 56.26, 56.72, 78.26, 94.42, 94.49, 95.74, 96.50, 107.72, 112.64, 116.78, 128.18, 133.18, 157.34, 157.52, 160.65, 161.46, 189.50. HRMS calcd for $C_{24}H_{31}O_8$ $[M + H]^+$ 447.2019; found 447.2014.

8-*n*-Pentyl-5,7,4'-tris(methoxymethoxy)flavanone (7c). Yield: 61%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.79 (br t, 3H, *J* = 7.0 Hz), 1.16-1.48 (m, 6H), 2.49 (br t, 2H, *J* = 7.3 Hz), 2.67 (dd, 1H, *J* = 2.9, 16.4 Hz), 2.99 (dd, 1H, *J* = 12.6, 16.4 Hz), 3.36, 3.37 and 3.39 (3s, 3H each s), 5.17, 5.19 and 5.26 (3s, 2H each s), 5.45 (dd, 1H, *J* = 2.9, 12.6 Hz), 6.48 (s, 1H), 7.05 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.51, 22.56, 22.70, 29.06, 31.81, 45.54, 56.25, 56.72, 78.28, 94.44, 95.76, 96.71, 107.75, 112.96, 116.73, 128.23, 133.14, 157.35, 157.46, 160.56, 161.39, 189.50. HRMS calcd for $C_{26}H_{35}O_8$ $[M + H]^+$ 475.2332; found 475.2320.

8-*n*-Heptyl-5,7,4'-tris(methoxymethoxy)flavanone (7d). Yield: 65%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.79 (br t, 3H, *J* = 7.0 Hz), 1.11-1.46 (m, 10H), 2.50 (br t, 2H, *J* = 6.8 Hz), 2.67 (dd, 1H, *J* = 2.9, 16.4 Hz), 2.98 (dd, 1H, *J* = 12.6, 16.4 Hz), 3.36, 3.38 and 3.40 (3s, 3H each s), 5.17, 5.19 and 5.26 (3s, 2H each s), 5.44 (dd, 1H, *J* = 2.9, 12.6 Hz), 6.48 (s, 1H), 7.04 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.58, 22.74, 22.90, 29.10, 29.34, 29.53, 31.84, 45.61, 56.22, 56.70, 56.72, 78.31, 94.49, 94.54, 95.81, 96.63, 107.79, 113.04, 116.72, 128.17, 133.18, 157.39, 157.47, 160.57, 161.40, 189.45. HRMS calcd for $C_{28}H_{39}O_8$ $[M + H]^+$ 503.2645; found 503.2633.

8-*n*-Nonyl-5,7,4'-tris(methoxymethoxy)flavanone (7e). Yield: 57%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, *J* = 7.0 Hz), 1.11-1.49 (m, 14H), 2.49 (br t, 2H, *J* = 6.8 Hz), 2.67 (dd, 1H, *J* = 2.6, 16.4 Hz), 2.98 (dd, 1H, *J* = 12.6, 16.4 Hz), 3.36, 3.37 and 3.39 (3s, 3H each s), 5.17, 5.19 and 5.26 (3s, 2H each s), 5.44 (dd, 1H, *J* = 2.6, 12.6 Hz), 6.48 (s, 1H), 7.04 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.64, 22.78, 29.36, 29.44, 29.52, 29.56, 31.95, 45.62, 56.23, 56.71, 78.28, 94.43, 95.73, 96.53, 107.72, 112.95, 116.69, 128.17, 133.17, 157.35, 157.46, 160.55, 161.39, 189.49. HRMS calcd for $C_{30}H_{43}O_8$ $[M + H]^+$ 531.2958; found 531.2944.

8-*n*-Undecyl-5,7,4'-tris(methoxymethoxy)flavanone (7f). Yield: 65%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, *J* = 7.0 Hz), 1.11-1.48 (m, 18H), 2.48 (br t, 2H, *J* = 6.8 Hz), 2.66 (dd, 1H, *J* = 2.9, 16.4 Hz), 2.97 (dd, 1H, *J* = 12.9, 16.4 Hz), 3.36, 3.37 and 3.39 (3s, 3H each s), 5.17, 5.18 and 5.26 (3s, 2H each s), 5.44 (dd, 1H, *J* = 2.9, 12.9 Hz), 6.47 (s, 1H), 7.03 (d, 2H, *J* = 8.8 Hz), 7.41 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.64, 22.79, 22.90, 29.35, 29.41, 29.46, 29.54, 29.62, 29.70, 29.75, 31.99, 45.63, 56.22, 56.70, 78.28, 94.44, 94.49, 95.75, 96.53, 107.73, 112.96, 116.68, 128.15, 133.17, 157.35, 157.47, 160.55, 161.39, 189.47. HRMS calcd for $C_{32}H_{47}O_8$ $[M + H]^+$ 559.3271; found 559.3247.

8-(3-Methylbutyl)-5,7,4'-tris(methoxymethoxy)flavanone (7g). Yield: 67%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br d, 6H, *J* = 6.5 Hz), 1.30 (br q, 2H, *J* = 7.3 Hz), 1.48 (br n, 1H, *J* = 6.5 Hz), 2.52 (br t, 2H, *J* = 7.0 Hz), 2.68 (dd, 1H, *J* = 2.9, 16.4 Hz), 2.98 (dd, 1H, *J* = 12.6, 16.4 Hz), 3.36, 3.38 and 3.40 (3s, 3H each s), 5.17, 5.18 and 5.26 (3s, 2H each s), 5.46 (dd, 1H, *J* = 2.9, 12.6 Hz), 6.47 (s, 1H), 7.04 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 21.02, 23.07, 23.20, 28.19, 38.83, 45.57, 56.27, 56.72, 78.27, 94.53, 94.62, 95.86, 96.74, 107.87, 113.28, 116.73, 128.71, 133.16, 157.37, 157.44, 160.52, 161.32, 189.44. HRMS calcd for $C_{26}H_{35}O_8$ $[M + H]^+$ 475.2332; found 475.2326.

8-(2-Methylpropyl)-5,7,4'-tris(methoxymethoxy)flavanone (7h). Yield: 57%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 and 0.83 (2d, 3H each d, *J* = 6.7 Hz each d), 1.81 (br n, 1H, *J* = 6.7 Hz), 2.39 (br d, 2H, *J* = 7.0 Hz), 2.65 (dd, 1H, *J* = 2.9, 16.4 Hz), 2.97 (dd, 1H, *J* = 12.9, 16.4 Hz), 3.36, 3.38 and 3.40 (3s, 3H each s), 5.18, 5.20 and 5.26 (3s, 2H each s), 5.43 (dd, 1H, *J* = 2.9, 12.9 Hz), 6.49 (s, 1H), 7.06 (d, 2H, *J* = 8.8 Hz), 7.41 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 23.07, 23.38, 28.83, 32.02, 45.79, 56.27, 56.73, 56.77, 78.28, 94.42, 94.55, 95.72, 96.32, 107.62, 111.92, 116.75, 128.09, 133.22, 157.31, 157.61, 160.89, 161.64, 189.54. HRMS calcd for $C_{25}H_{33}O_8$ $[M + H]^+$ 461.2175; found 461.2173.

8-(2,2-Dimethylpropyl)-5,7,4'-tris(methoxymethoxy)flavanone (7i). Yield: 61%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 2.45 (d, 1H, *J* = 12.9 Hz), 2.49 (d, 1H, *J* = 12.9 Hz), 2.60 (dd, 1H, *J* = 2.6, 16.4 Hz), 2.97 (dd, 1H, *J* = 13.2, 16.4 Hz), 3.37, 3.38 and 3.41 (3s, 3H each s), 5.19, 5.20 and 5.22 (3s, 2H each s), 5.38 (dd, 1H, *J* = 2.6, 13.2 Hz), 6.51 (s, 1H), 7.05 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.60, 33.72, 35.69, 46.09, 56.29, 56.75, 56.94, 78.55, 94.49, 94.94, 95.74, 96.35, 107.64, 110.48, 116.73, 128.29, 133.15, 157.36, 157.82, 161.71, 162.21, 189.61. HRMS calcd for $C_{26}H_{35}O_8$ $[M + H]^+$ 475.2332; found 475.2329.

8-Benzyl-5,7,4'-tris(methoxymethoxy)flavanone (7j). Yield: 69%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.68 (dd, 1H, *J* = 2.9, 16.4 Hz), 3.03 (dd, 1H, *J* = 12.6, 16.4 Hz), 3.25, 3.35 and 3.39 (3s, 3H each s), 3.81 (d, 1H, *J* = 14.1 Hz), 3.86 (d, 1H, *J* = 14.1 Hz), 5.18, 5.19 and 5.27 (3s, 2H each s), 5.48 (dd, 1H, *J* = 2.9, 12.6 Hz), 6.50 (s, 1H), 7.01 (d, 2H, *J* = 8.5 Hz), 7.07-7.24 (m, 5H), 7.35 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.86, 45.42, 56.26, 56.70, 56.75, 78.51, 94.50, 95.78, 96.47, 107.80, 111.69, 116.74, 126.33, 128.35, 128.78, 128.88, 132.91, 141.38, 157.40, 158.01, 160.54, 161.31, 189.31. HRMS calcd for $C_{28}H_{31}O_8$ $[M + H]^+$ 495.2019; found 495.2012.

7. General procedure for the preparation of 8-alkylnaringenins (**8a-j**)

To a stirring solution of 8-alkyl-5,7,4'-tris(methoxymethoxy)flavanone (**7a-j**) in MeOH (15 mL/mmol), 3 M HCl (5 mL/mmol) was added dropwise.[4] The reaction mixture was heated to reflux for 1 h (or until completion of the reaction, as monitored by TLC). The mixture was then poured into H_2O and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc), to afford **8a-j**.

8-Methylnaringenin (8a). Yield: 93%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.84 (s, 3H), 2.70 (dd, 1H, *J* = 2.9, 16.9 Hz), 3.19 (dd, 1H, *J* = 12.6, 16.9 Hz), 5.41 (dd, 1H, *J* = 2.9,

12.6 Hz), 5.96 (s, 1H), 6.78 (d, 2H, *J* = 8.5 Hz), 7.30 (d, 2H, *J* = 8.5 Hz), 9.57, 10.75 and 12.08 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 8.30, 42.51, 78.72, 95.76, 102.38, 103.21, 115.86, 128.72, 129.87, 158.26, 160.48, 161.63, 165.32, 197.40. HRMS calcd for $C_{16}H_{13}O_5$ [M - H]$^-$ 285.0763; found 285.0754. Anal. ($C_{16}H_{14}O_5$) C, H.

8-*n*-Propylnaringenin (8b). Yield: 88%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.80 (br t, 3H, *J* = 7.3 Hz), 1.39 (m, 2H), 2.37 (br t, 2H, *J* = 7.3 Hz), 2.70 (dd, 1H, *J* = 2.9, 16.9 Hz), 3.16 (dd, 1H, *J* = 12.5, 16.9 Hz), 5.39 (dd, 1H, *J* = 2.9, 12.5 Hz), 5.96 (s, 1H), 6.78 (d, 2H, *J* = 8.8 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 9.57, 10.65 and 12.12 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.54, 22.60, 24.56, 42.65, 78.69, 95.90, 102.39, 108.18, 115.87, 128.54, 130.01, 158.22, 160.67, 161.77, 165.31, 197.46. HRMS calcd for $C_{18}H_{17}O_5$ [M - H]$^-$ 313.1076; found 313.1061. Anal. ($C_{18}H_{18}O_5$) C, H.

8-*n*-Pentylnaringenin (8c). Yield: 95%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.78 (br t, 3H, *J* = 6.8 Hz), 1.12-1.44 (m, 6H), 2.38 (br t, 2H, *J* = 7.0 Hz), 2.71 (dd, 1H, *J* = 2.9, 16.9 Hz), 3.15 (dd, 1H, *J* = 12.6, 16.9 Hz), 5.38 (dd, 1H, *J* = 2.9, 12.6 Hz), 5.95 (s, 1H), 6.77 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 9.55, 10.66 and 12.10 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.57, 22.43, 22.59, 29.00, 31.74, 42.63, 78.70, 95.92, 102.41, 108.48, 115.82, 128.54, 129.99, 158.21, 160.58, 161.73, 165.25, 197.42. HRMS calcd for $C_{20}H_{21}O_5$ [M - H]$^-$ 341.1389; found 341.1390. Anal. ($C_{20}H_{22}O_5$) C, H.

8-*n*-Heptylnaringenin (8d). Yield: 91%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.80 (br t, 3H, *J* = 7.0 Hz), 1.11-1.41 (m, 10H), 2.38 (br t, 2H, *J* = 7.0 Hz), 2.71 (dd, 1H, *J* = 2.9, 16.9 Hz), 3.14 (dd, 1H, *J* = 12.5, 16.9 Hz), 5.38 (dd, 1H, *J* = 2.9, 12.5 Hz), 5.95 (s, 1H), 6.77 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 9.54, 10.63 and 12.09 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.62, 22.45, 22.75, 29.15, 29.30, 29.44, 31.89, 42.68, 78.70, 95.94, 102.40, 108.51, 115.81, 128.47, 130.02, 158.21, 160.59, 161.73, 165.30, 197.38. HRMS calcd for $C_{22}H_{25}O_5$ [M - H]$^-$ 369.1702; found 369.1689. Anal. ($C_{22}H_{26}O_5$) C, H.

8-*n*-Nonylnaringenin (8e). Yield: 94%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.82 (br t, 3H, *J* = 7.0 Hz), 1.11-1.42 (m, 14H), 2.37 (br t, 2H, *J* = 7.3 Hz), 2.70 (dd, 1H, *J* = 2.9, 16.9 Hz), 3.15 (dd, 1H, *J* = 12.5, 16.9 Hz), 5.38 (dd, 1H, *J* = 2.9, 12.5 Hz), 5.94 (s, 1H), 6.77 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 9.55, 10.70 and 12.11 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.65, 22.43, 22.79, 29.27, 29.38, 29.44, 29.49, 29.61, 31.97, 42.71, 78.70, 95.92, 102.41, 108.49, 115.80, 128.46, 130.00, 158.21, 160.60, 161.73, 165.25, 197.41. HRMS calcd for $C_{24}H_{29}O_5$ [M - H]$^-$ 397.2015; found 397.2018. Anal. ($C_{24}H_{30}O_5$) C, H.

8-*n*-Undecylnaringenin (8f). Yield: 90%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.83 (br t, 3H, *J* = 7.0 Hz), 1.11-1.42 (m, 18H), 2.37 (br t, 2H, *J* = 7.0 Hz), 2.70 (dd, 1H, *J* = 2.9, 17.0 Hz), 3.14 (dd, 1H, *J* = 12.6, 17.0 Hz), 5.38 (dd, 1H, *J* = 2.9, 12.6 Hz), 5.94 (s, 1H), 6.76 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 9.54, 10.66 and 12.10 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 14.63, 22.45, 22.77, 29.27, 29.38, 29.44, 29.47, 29.63, 29.68, 31.97, 42.72, 78.70, 95.95, 102.43, 108.51, 115.82, 128.44, 130.01, 158.22, 160.60, 161.74, 165.25, 197.38. HRMS calcd for $C_{26}H_{33}O_5$ [M - H]$^-$ 425.2328; found 425.2341. Anal. ($C_{26}H_{34}O_5$) C, H.

8-(3-Methylbutyl)naringenin (8g). Yield: 96%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 (br d, 6H, *J* = 6.5 Hz), 1.24 (br q, 2H, *J* = 7.0 Hz), 1.43 (br n, 1H, *J* = 6.5 Hz), 2.39 (br t, 2H, *J* = 7.0 Hz), 2.71 (dd, 1H, *J* = 2.6, 17.3 Hz), 3.15 (dd, 1H, *J* = 12.9, 17.3 Hz), 5.40 (dd, 1H, *J* = 2.6, 12.9 Hz), 5.95 (s, 1H), 6.77 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 2H, *J* = 8.5 Hz),

9.54, 10.66 and 12.09 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 20.54, 23.13, 23.23, 28.05, 38.76, 42.62, 78.66, 95.92, 102.45, 108.69, 115.78, 128.49, 129.98, 158.16, 160.52, 161.69, 165.17, 197.41. HRMS calcd for $C_{20}H_{21}O_5$ [M - H]$^-$ 341.1389; found 341.1386. Anal. ($C_{20}H_{22}O_5$) C, H.

8-(2-Methylpropyl)naringenin (8h). Yield: 96%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.77 and 0.80 (2d, 3H each d, *J* = 6.5 Hz each d), 1.76 (br n, 1H, *J* = 6.8 Hz), 2.27 (br d, 2H, *J* = 7.0 Hz), 2.68 (dd, 1H, *J* = 2.9, 17.0 Hz), 3.15 (dd, 1H, *J* = 12.9, 17.0 Hz), 5.37 (dd, 1H, *J* = 2.9, 12.9 Hz), 5.96 (s, 1H), 6.78 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 9.56, 10.66 and 12.14 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 22.97, 23.31, 28.64, 31.62, 42.80, 78.72, 95.91, 102.34, 107.59, 115.86, 128.47, 130.05, 158.19, 160.89, 161.82, 165.51, 197.53. HRMS calcd for $C_{19}H_{19}O_5$ [M - H]$^-$ 327.1232; found 327.1236. Anal. ($C_{19}H_{20}O_5$) C, H.

8-(2,2-Dimethylpropyl)naringenin (8i). Yield: 95%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 9H), 2.33 (d, 1H, *J* = 12.9 Hz), 2.36 (d, 1H, *J* = 12.9 Hz), 2.62 (dd, 1H, *J* = 2.9, 17.0 Hz), 3.15 (dd, 1H, *J* = 13.2, 17.0 Hz), 5.32 (dd, 1H, *J* = 2.9, 13.2 Hz), 5.96 (s, 1H), 6.77 (d, 2H, *J* = 8.8 Hz), 7.28 (d, 2H, *J* = 8.8 Hz), 9.54, 10.66 and 12.21 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 30.53, 33.84, 35.36, 43.11, 78.93, 95.94, 102.29, 106.25, 115.82, 128.63, 130.03, 158.19, 161.48, 161.94, 166.29, 197.54. HRMS calcd for $C_{20}H_{21}O_5$ [M - H]$^-$ 341.1389; found 341.1397. Anal. ($C_{20}H_{22}O_5$) C, H.

8-Benzylnaringenin (8j). Yield: 89%. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.72 (dd, 1H, *J* = 2.6, 17.0 Hz), 3.19 (dd, 1H, *J* = 12.5, 17.0 Hz), 3.71 (br s, 2H), 5.43 (dd, 1H, *J* = 2.6, 12.5 Hz), 5.98 (s, 1H), 6.75 (d, 2H, *J* = 8.5 Hz), 7.06-7.20 (m, 5H), 7.23 (d, 2H, *J* = 8.5 Hz), 9.56, 10.88 and 12.13 (3s, 1H each s); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 28.44, 42.52, 78.91, 96.04, 102.47, 107.47, 115.84, 126.19, 128.62, 128.69, 128.89, 129.77, 141.78, 158.24, 160.63, 162.18, 165.15, 197.40. HRMS calcd for $C_{22}H_{17}O_5$ [M - H]$^-$ 361.1076; found 361.1077. Anal. ($C_{22}H_{18}O_5$) C, H.

Combustion analysis data of target compounds

Compound	Formula		C	H
8a	$C_{16}H_{14}O_5$	calcd	67.13	4.93
		found	66.89	4.98
8b	$C_{18}H_{18}O_5$	calcd	68.78	5.77
		found	68.65	5.73
8c	$C_{20}H_{22}O_5$	calcd	70.16	6.48
		found	70.09	6.49
8d	$C_{22}H_{26}O_5$	calcd	71.33	7.07
		found	71.26	7.28
8e	$C_{24}H_{30}O_5$	calcd	72.34	7.59
		found	72.33	7.46
8f	$C_{26}H_{34}O_5$	calcd	73.21	8.03
		found	73.17	8.05
8g	$C_{20}H_{22}O_5$	calcd	70.16	6.48
		found	69.81	6.77
8h	$C_{19}H_{20}O_5$	calcd	69.50	6.14
		found	69.24	6.12
8i	$C_{20}H_{22}O_5$	calcd	70.16	6.48
		found	70.23	6.43
8j	$C_{22}H_{18}O_5$	calcd	72.92	5.01
		found	73.17	5.20

References

1. Jain, A. C.; Gupta, R. C.; Sarpal, P. D. Synthesis of (±)-lupinifolin, di-O-methyl xanthohumol and isoxanthohumol and related compounds. *Tetrahedron* **1978**, *34*, 3563-3567.
2. Carey, F. A.; Tremper, H. S. Carbonium ion-silane hydride transfer reactions. V. *tert*-Alkyl cations. *J. Org. Chem.* **1971**, *36*, 758-761.
3. Munson, M. C.; Garcia-Echeverria, C.; Albericio, F.; Barany, G. *S*-2,4,6-Trimethoxybenzyl (Tmob): a novel cysteine protecting group for the N^{α}-9-fluorenylmethoxycarbonyl (Fmoc) strategy of peptide synthesis. *J. Org. Chem.* **1992**, *57*, 3013-3018.
4. Huang, C.; Zhang, Z.; Li, Y. Total synthesis of (*R*,*S*)-sophoraflavanone C. *J. Nat. Prod*. **1998**, *61*, 1283-1285.