The spectral data of the synthetic compounds

[(1E,1'E)-(4-Oxo-1-propionylpiperidine-3,5-diylidene)bis(methanylylidene)]bis(2-methoxy-4,1-phenylene)dipropionate (S1): Yellow powder, 8.4% yield, mp 146.6-148.5 ^{o}C, HPLC purity (methanol: water) = 83.22. ^{1}H-NMR ($CDCl_3$) δ: 7.580 (s, 2H, *β*-H × 2), 7.134-7.212 (m, 4H, H-3 × 2, H-5 × 2), 6.910 (d, *J* = 8.4 Hz, 2H, H-6 × 2), 3.824 (t, *J* = 5.4 Hz, 10H, 2-OCH_3 × 2, 2′-CH_2, 6′-CH_2), 2.607 (q, *J* = 7.8 Hz, 6H, -C*H*$_2$$CH_3$ × 3), 1.144 (t, *J* = 7.8 Hz, 9H, -CH_3 × 3). ESI-MS m/z: 536.8 $(M+1)^+$, calcd for $C_{30}H_{34}NO_3$: 535.2.

[(1E,1'E)-(4-Oxo-2H-pyran-3,5(4H,6H)-diylidene)bis(methanylylidene)]bis(2-methoxy-4,1-phenylene)dipropionate (S2): Yellow powder, 20.1% yield, mp 161.3-164.3 ^{o}C, HPLC purity (methanol: water) = 62.92. ^{1}H-NMR ($CDCl_3$) δ: 7.788 (s, 2H, *β*-H × 2), 7.089 (d, *J* = 7.8 Hz, 2H, H-6 × 2), 6.929 (s, 2H, H-3 × 2), 6.880 (d, *J* = 8.4 Hz, 2H, H-5 × 2), 4.933 (s, 4H, 2′-CH_2, 6′-CH_2), 3.855 (s, 6H, 2-OCH_3 × 2), 2.628 (q, *J* = 7.8 Hz, 4H, -C*H*$_2$$CH_3$ × 2), 1.284 (t, *J* = 7.8 Hz, 6H, -CH_3 × 2). ESI-MS m/z: 481.8 $(M+1)^+$, calcd for $C_{27}H_{29}O_8$: 480.2.

[(1Z,1'Z)-(4-Oxo-2H-thiopyran-3,5(4H,6H)-diylidene)bis(methanylylidene)]bis(2-methoxy-4,1-phenylene)dipropionate (S3): Yellow powder, 17.7% yield, mp 142.3-145.8 ^{o}C, HPLC purity (methanol: water) = 100.00. ^{1}H-NMR ($CDCl_3$) δ: 7.727 (s, 2H, *β*-H × 2), 7.080 (d, *J* = 7.8 Hz, 2H, H-6 × 2), 6.988 (t, *J* = 8.4 Hz, 4H, H-3 × 2, H-5 × 2), 3.918 (s, 4H, 2′-CH_2, 6′-CH_2), 3.847 (s, 6H, 2-OCH_3 × 2), 2.631 (q, *J* = 7.8 Hz, 4H, -C*H*$_2$$CH_3$ × 2), 1.285 (t, *J* = 8.4 Hz, 6H, -CH_3 × 2). ESI-MS m/z: 498.3 $(M+1)^+$, calcd for $C_{27}H_{29}O_8$: 496.2.

[(1E,1'E)-(4-Oxo-2H-pyran-3,5(4H,6H)-diylidene)bis(methanylylidene)]bis(2-methoxy-4,1-phenylene)bis(2-methylpropanoate) (S4): Yellow powder, 27.7% yield, mp 142.9-145.1 ^{o}C, HPLC purity (methanol: water) = 99.80. ^{1}H-NMR ($CDCl_3$) δ: 7.789 (s, 2H, *β*-H × 2), 7.078 (d, *J* = 8.4 Hz, 2H, H-6 × 2), 6.923 (d, *J* = 1.8 Hz, 2H, H-3 × 2), 6.880 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 2H, H-5 × 2), 4.933 (s, 4H, 2′-CH_2, 6′-CH_2),

3.847 (s, 6H, 2-OCH_3 × 2), 2.827-2.874 (m, 2H, -C<u>*H*</u>$(CH_3)_2$ × 2), 1.334 (d, *J* = 6.6 Hz, 12H, -CH(C<u>*H*₃</u>)$_2$ × 2). ESI-MS m/z: 509.8 $(M+1)^+$, calcd for $C_{29}H_{33}O_8$: 508.2.

[(1Z,1'Z)-(4-Oxo-2H-thiopyran-3,5(4H,6H)-diylidene)bis(methanylylidene)]bis(2-methoxy-4,1-phenylene)bis(2-methylpropanoate) (S5): Yellow powder, 30.9% yield, mp 149.8-152.6 °C, HPLC purity (methanol: water) = 100.00. ^{1}H-NMR ($CDCl_3$) δ: 7.728 (s, 2H, *β*-H × 2), 7.067 (d, *J* = 8.4 Hz, 2H, H-6 × 2), 6.984 (t, *J* = 8.4 Hz, 4H, H-3 × 2, H-5 × 2), 3.917 (s, 4H, 2′-CH_2, 6′-CH_2), 3.839 (s, 6H, 2-OCH_3 × 2), 2.828-2.874 (m, 2H, -C<u>*H*</u>$(CH_3)_2$ × 2), 1.335 (d, *J* = 6.6 Hz, 12H, -CH(C<u>*H*₃</u>)$_2$ × 2). ESI-MS m/z: 526.6 $(M+1)^+$, calcd for $C_{29}H_{33}O_7S$: 524.2.

(2E,5E)-2-(4-Hydroxy-3-methoxybenzylidene)-5-(4-methoxybenzylidene)cyclopentanone (AS1): Orange yellow powder, 11.1% yield, mp 166.8-169.7 °C, HPLC purity (methanol: water) = 95.33. ^{1}H-NMR (d_6-DMSO) δ: 7.644 (d, *J* = 8.4 Hz , 2H, H-2″, H-6″), 7.376 (s, 2H, *β*-H, *β*′-H), 7.250 (s, 1H, H-2′), 7.169 (d, *J* = 8.4 Hz, 1H, H-6′), 7.053 (d, *J* = 8.4 Hz, 2H, H-3″, H-5″), 6.890 (d, *J* = 8.4 Hz, 1H, H-5′), 3.838 (s, 3H, 4″-OCH_3), 3.818 (s, 3H, 3′-OCH_3), 3.054 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 337.0 $(M+1)^+$, calcd for $C_{21}H_{21}O_4$: 336.1.

(2E,5E)-2-(4-Hydroxy-3-methoxybenzylidene)-5-(4-hydroxybenzylidene)cyclopentanone (AS2): Yellow powder, 10.1% yield, mp 147.5-150.5 °C, HPLC purity (methanol: water) = 97.07. ^{1}H-NMR (d_6-DMSO) δ: 7.539 (d, *J* = 8.4 Hz, 2H, H-2″, H-6″), 7.347 (d, *J* = 8.4 Hz, 2H, *β*-H, *β*′-H), 7.246 (s, 1H, H-2′), 7.164 (d, *J* = 8.4 Hz, 1H, H-6′), 6.882 (t, *J* = 7.8 Hz, 3H, H-5, H-3″, H-5″), 3.837 (s, 3H, 3′-OCH_3), 3.016-3.065 (m, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 323.0 $(M+1)^+$, calcd for $C_{20}H_{19}O_4$: 322.1.

(2E,5E)-2-(2,5-Dimethoxybenzylidene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS3): Yellow powder, 16.4% yield, mp 175.3-178.1 °C, HPLC purity (methanol: water) = 93.16. ^{1}H-NMR (d_6-DMSO) δ: 7.954 (s, 1H, *β*′-H), 7.533 (s, 1H, *β*-H), 7.194 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, H-6′), 7.101 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 2H, H-2′, H-5′), 6.983 (d, *J* = 8.4 Hz, 1H, H-3″), 6.903 (dd, J_1 = 3.0 Hz, J_2 =

8.4 Hz, 1H, H-4″), 6.865 (d, *J* = 3.0 Hz, 1H, H-6″), 3.944 (s, 3H, 3′-OCH_3), 3.844 (s, 3H, 2″-OCH_3), 3.812 (s, 3H, 5″- OCH_3), 3.064 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 367.0 $(M+1)^+$, calcd for $C_{22}H_{23}O_5$: 366.1.

(2E,5E)-2-(2-Bromobenzylidene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS4): Yellow powder, 13.1% yield, mp 90.6-93.8 °C, HPLC purity (methanol: water) = 95.71. ^{1}H-NMR (d_6-DMSO) δ: 7.821 (s, 1H, *β*′-H), 7.660 (d, *J* = 7.8 Hz, 1H, H-3″), 7.333 (s, 2H, *β*-H, H-5″), 7.202 (d, *J* = 7.8 Hz, 2H, H-4″, H-6″), 7.136 (d, *J* = 7.8 Hz, 2H, H-5′, H-6′), 7.094 (s, 1H, H-2′), 3.950 (s, 3H, 3′-OCH_3), 3.006-3.064 (m, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 385.0 $(M+1)^+$, calcd for $C_{20}H_{18}BrO_3$: 384.0.

(2E,5E)-2-(3,4-Dimethoxybenzylidene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS5): Yellow powder, 13.3% yield, mp 138.3-141.1 °C, HPLC purity (methanol: water) = 89.00. ^{1}H-NMR (d_6-DMSO) δ: 7.386 (s, 1H, *β*′-H), 7.375 (s, 1H, *β*-H), 7.275 (d, *J* = 5.4 Hz, 2H, H-2″, H-6″), 7.255 (d, *J* = 1.2 Hz, 1H, H-2′), 7.170 (d, *J* = 8.4 Hz, 1H, H-6′), 7.075 (d, *J* = 8.4 Hz, 1H, H-5′), 6.895 (d, *J* = 8.4 Hz, 1H, H-5″), 3.840 (s, 3H, 3′-OCH_3), 3.823 (d, *J* = 4.2 Hz, 6H, 3″,4″-OCH_3), 3.083 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 366.9 $(M+1)^+$, calcd for $C_{22}H_{23}O_5$: 366.1.

(2E,5E)-2-(4-Ethoxybenzylidene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS6): Yellow powder, 14.1% yield, mp 161-164.8 °C, HPLC purity (methanol: water) = 95.10. ^{1}H-NMR (d_6-DMSO) δ: 7.628 (d, *J* = 9.0 Hz, 2H, H-2″, H-6″), 7.372 (s, 2H, *β*′-H, *β*-H), 7.249 (d, *J* = 1.2 Hz, 1H, H-2′), 7.168 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-6′), 7.033 (d, *J* = 8.4 Hz, 2H, H-3″, H-5″), 6.889 (d, *J* = 7.8 Hz, 1H, H-5′), 4.092 (q, *J* = 7.2 Hz, 2H, -OC$\underline{H_2}$$CH_3$), 3.839 (s, 3H, 3′-$OCH_3$), 3.052 (s, 4H, 3-$CH_2$, 4-$CH_2$), 1.347 (t, *J* = 7.2 Hz, 3H, -$OCH_2C\underline{H_3}$). ESI-MS m/z: 351.0 $(M+1)^+$, calcd for $C_{22}H_{23}O_4$: 350.2.

(2E,5E)-2-(2,3-Dimethoxybenzylidene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS7): Yellow powder, 11.7% yield, mp 181.8-184.5 °C, HPLC purity (methanol: water) = 99.71. ^{1}H-NMR (d_6-DMSO) δ: 7.667 (s, 1H, *β*′-H), 7.404 (s, 1H, *β*-H), 7.249 (d, *J* = 8.4 Hz, 2H, H-5″, H-6″), 7.166-7.192 (m, 2H, H-2′, H-6′), 7.143 (d, *J* = 7.2 Hz, 1H, H-5′), 6.894 (d, *J* = 7.8 Hz, 1H, H-4″), 3.839 (d, *J* = 1.8 Hz,

6H, 2″,3″-OCH_3), 3.770 (s, 3H, ¸3′-OCH_3), 3.041 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 366.8 $(M+1)^+$, calcd for $C_{22}H_{23}O_5$: 366.1.

(2E,5E)-2-[(2,4-Dichlorophenyl)methylidene]-5-[(4-hydroxy-3-methoxyphenyl)methylidene]cyclopentan-1-one (AS8): Orange yellow powder, 13.5% yield, mp 138.7-141.3 °C, HPLC purity (methanol: water) = 92.07. ^{1}H-NMR ($CDCl_3$) δ: 7.810 (s, 1H, *β*′-H), 7.569 (s, 1H, *β*-H), 7.508 (d, *J* = 8.4 Hz, 1H, H-6″), 7.482 (d, *J* = 2.4 Hz, 1H, H-3″), 7.295 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5″), 7.201 (d, *J* = 1.8 Hz, 1H, H-2′), 7.089 (d, *J* = 8.4 Hz, 1H, H-6′), 6.991 (d, *J* = 8.4 Hz, 1H, H-5′), 3.951 (s, 3H, 3′-OCH_3), 3.026-3.050 (m, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 375.0 $(M+1)^+$, calcd for $C_{20}H_{17}Cl_2O$: 374.0.

(2E,5E)-2-[(4-Hydroxy-3-methoxyphenyl)methylidene]-5-[(3,4,5-trimethoxyphenyl)methylidene]cyclopentan-1-one (AS9): Orange yellow powder, 19.5% yield, mp 159.9-162.7 °C, HPLC purity (methanol: water) = 73.19. ^{1}H-NMR ($CDCl_3$) δ: 7.508-7.549 (m, 2H, *β*-H, *β*′-H), 7.206 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-6′), 7.105 (d, *J* = 1.2 Hz, 1H, H-2′), 6.994 (d, *J* = 8.4 Hz, 1H, H-5′), 6.849 (s, 2H, H-2″, H-6″), 3.907-3.949 (m, 12H, 3′-OCH_3, 3″,4″,5″-OCH_3), 3.140 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 397.0 $(M+1)^+$, calcd for $C_{23}H_{25}O_6$: 396.2.

(2E,5E)-2-[(4-Hydroxy-3-methoxyphenyl)methylidene]-5-[(3-hydroxyphenyl)methylidene]cyclopentan-1-one (AS10): Orange yellow powder, 16.4% yield, mp 193.4-196.3 °C, HPLC purity (methanol: water) = 93.24. ^{1}H-NMR (d_6-DMSO) δ: 7.398 (s, 1H, H-6″), 7.259-7.280 (m, 2H, *β*-H, *β*′-H), 7.303 (s, 1H, H-2′), 7.184 (d, *J* = 8.4 Hz, 1H, H-5″), 7.099 (d, *J* = 7.8 Hz, 1H, H-6′), 7.073 (s, 1H, H-2″), 6.896 (d, *J* = 8.4 Hz, 1H, H-5′), 6.832 (d, *J* = 8.4 Hz, 1H, H-4″), 3.840 (s, 3H, 3′-OCH_3), 3.065 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 322.9 $(M+1)^+$, calcd for $C_{20}H_{20}O_4$: 322.1.

(2E,5E)-2-(3,4-Dihydroxybenzylidene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS11): Green powder, 70.1% yield, mp 260 °C carbonization, HPLC purity (methanol: water) = 88.20. ^{1}H-NMR (d_6-DMSO) δ: 7.345 (s, 1H, *β*′-H), 7.248 (d, *J* = 2.4 Hz, 2H, *β*-H, H-2″), 7.162 (d, *J* = 8.4 Hz, 1H, H-6″),

7.120 (d, J = 1.8 Hz, 1H, H-2′), 7.009 (d, J = 8.4 Hz, 1H, H-6′), 6.892 (d, J = 8.4 Hz, 1H, H-5′), 6.844 (d, J = 8.4 Hz, 1H, H-5″), 3.837 (s, 3H, 3′-OCH_3), 2.500 (s, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 338.9 $(M+1)^+$, calcd for $C_{20}H_{20}O_5$: 338.1.

(2E,5E)-2-(4-Hydroxy-3-methoxybenzylidene)-5-[(5-methylthiophen-2-yl)methylene]cyclopentanone (AS12): Yellow powder, 20.1% yield, mp 167.2-170.8 ^oC, HPLC purity (methanol: water) = 93.59. ^1H-NMR (d_6-DMSO) δ: 7.586 (s, 1H, H-3″), 7.421 (s, 1H, β'-H), 7.343 (s, 1H, β-H), 7.245 (s, 1H, H-4″), 7.164 (d, J = 8.4 Hz, 1H, H-6′), 6.970 (d, J = 3.0 Hz, 1H, H-2′), 6.889 (d, J = 8.4 Hz, 1H, H-5′), 3.837 (s, 3H, 3′-OCH_3), 3.089 (t, J = 4.2 Hz, 2H, 3-CH_2), 2.895 (t, J = 4.2 Hz, 2H, 4-CH_2). ESI-MS m/z: 327.9 $(M+1)^+$, calcd for $C_{19}H_{19}O_3S$: 326.1.

(2E,5E)-2-(4-Hydroxy-3-methoxybenzylidene)-5-(thiophen-2-ylmethylene)cyclopentanone (AS13): Yellow powder, 3.2% yield, mp 167.8-172.0 ^oC, HPLC purity (methanol: water) = 98.45. ^1H-NMR (d_6-DMSO) δ: 7.904 (d, J = 5.4 Hz, 1H, H-5″), 7.685 (s, 1H, H-3″), 7.614 (s, 1H, H-4″), 7.369 (s, 1H, β'-H), 7.264 (t, J = 8.4 Hz, 2H, β-H, H-6′), 7.176 (t, J_1 = 1.8 Hz, J_2 = 7.2 Hz, 2H, H-2′, H-5′), 3.841 (s, 3H, 3′-OCH_3), 3.105-3.133 (m, 2H, 3-CH_2), 2.907-2.952 (m, 2H, 4-CH_2). ESI-MS m/z: 313.9 $(M+1)^+$, calcd for $C_{18}H_{17}O_3S$: 312.1.

(2E,5E)-2-(Furan-2-ylmethylene)-5-(4-hydroxy-3-methoxybenzylidene)cyclopentanone (AS14): Yellow powder, 22.5% yield, mp 139.5-142.3 ^oC, HPLC purity (methanol: water) = 97.56. ^1H-NMR (d_6-DMSO) δ: 7.943 (s, 1H, H-5″), 7.352 (s, 2H, H-3″, H-4″), 7.245 (s, 1H, β'-H), 7.208 (s, 1H, β-H), 6.957 (d, J = 3.6 Hz, 1H, H-2′), 6.889 (d, J = 7.8 Hz, 1H, H-6′), 6.856 (d, J = 8.4 Hz, 1H, H-5′), 3.835 (s, 3H, 3′-OCH_3), 3.003-3.065 (m, 4H, 3-CH_2, 4-CH_2). ESI-MS m/z: 298.1 $(M+1)^+$, calcd for $C_{18}H_{17}O_4$: 296.1.

(2E,5E)-2-[(4-Hydroxy-3-methoxyphenyl)methylidene]-5-[(1-methyl-1H-pyrrol-2-yl)methylidene]cyclopentan-1-one (AS15): Orange yellow powder, 26.8% yield, mp 190.0-192.5 ^oC, HPLC purity (methanol:

water) = 97.28. ^{1}H-NMR (d_6-DMSO) δ: 7.404 (s, 1H, β'-H), 7.309 (s, 1H, β-H), 7.241 (s, 1H, H-5″), 7.130 (s, 1H, H-2′), 7.094 (d, J = 8.4 Hz, 2H, H-5′, H-6′), 6.598 (d, J = 3.6 Hz, 1H, H-4″), 6.255 (d, J = 3.0 Hz, 1H, H-3″), 3.838 (s, 3H, 3′-OCH_3), 3.813 (s, 4H, 3-CH_2, 4-CH_2), 3.764 (s, 3H, N-CH_3). ESI-MS m/z: 309.8 $(M+1)^+$, calcd for $C_{19}H_{20}NO_3$: 309.1.

2-Methoxy-4-{(E)-[(E)-3-(4-methoxybenzylidene)-2-oxocyclopentylidene]methyl}phenyl propionate (AS16): Yellow powder, 5.1% yield, mp 167.4-170.3 °C, HPLC purity (methanol: water) = 88.51. ^{1}H-NMR ($CDCl_3$) δ: 7.581 (d, J = 9.0 Hz, 2H, H-2″, H-6″), 7.566 (s, 1H, β-H), 7.534 (s, 1H, β'-H), 7.214(dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.170 (s, 1H, H-3), 7.097 (d, J = 8.4 Hz, 1H, H-6), 6.972 (d, J = 9.0 Hz, 2H, H-3″, H-5″), 3.875 (s, 3H, 2-OCH_3), 3.864 (s, 3H, 4″-OCH_3), 3.101 (s, 4H, 4′-CH_2, 5′-CH_2), 2.617-2.655 (m, 2H, -COC$\underline{H_2}$$CH_3$), 1.284 (t, J = 7.2 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 392.9 $(M+1)^+$, calcd for $C_{24}H_{25}O_5$: 392.2.

4-{(E)-[(E)-3-(4-Fluorobenzylidene)-2-oxocyclopentylidene]methyl}-2-methoxyphenyl propionate (AS17): Yellow powder, 53.7% yield, mp 158.6-161.4 °C, HPLC purity (methanol: water) = 79.53. ^{1}H-NMR ($CDCl_3$) δ: 7.487-7.531 (m, 4H, β-H, β'-H, H-2″, H-6″), 7.145 (t, J = 8.4 Hz, 1H, H-5′), 7.097 (s, 1H, H-3′), 7.072 (d, J = 9.0 Hz, 2H, H-3″, H-5″), 7.034 (d, J = 8.4 Hz, 1H, H-6′), 3.806 (s, 3H, 2′-OCH_3), 3.035 (t, J = 1.8 Hz, 4H, 3-CH_2, 4-CH_2), 2.548-2.586 (m, 2H, -COC$\underline{H_2}$$CH_3$), 1.219 (t, J = 1.8 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 380.8 $(M+1)^+$, calcd for $C_{23}H_{22}FO_4$: 380.1.

2-Methoxy-4-{(E)-[(E)-3-(4-methoxy-3-(propionyloxy)benzylidene)-2-oxocyclopentylidene]methyl}phenyl propionate (AS18): Yellow powder, 22.3% yield, mp 145-148.5 °C, HPLC purity (methanol: water) = 88.36. ^{1}H-NMR ($CDCl_3$) δ: 7.531 (s, 2H, β-H, β'-H), 7.459 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, H-6″), 7.315 (d, J = 1.8 Hz, 1H, H-3), 7.208 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, H-5′), 7.164 (s, 1H, H-2″), 7.098 (d, J = 7.8 Hz, 1H, H-6), 7.020 (d, J = 8.4 Hz, 1H, H-5″), 3.879 (s, 3H, 4″-OCH_3), 3.872 (s, 3H, 2-OCH_3), 3.084-3.102 (m, 4H, 4′-CH_2, 5′-CH_2), 2.616-2.665 (m, 4H, -COC$\underline{H_2}$$CH_3$ × 2), 1.275-1.308 (m, 6H,

-$COCH_2C\underline{H_3}$ × 2). ESI-MS m/z: 465.5 $(M+1)^+$, calcd for $C_{27}H_{29}O_7$: 464.2.

2-Methoxy-4-{(E)-[(E)-2-oxo-3-(2-(propionyloxy)benzylidene)cyclopentylidene]methyl}phenyl propionate (AS19): Yellow powder, 30.2% yield, mp 105.9-107.3 °C, HPLC purity (methanol: water) = 81.19. ^{1}H-NMR ($CDCl_3$) δ: 7.561 (s, 2H, H-3″, H-6″), 7.448 (s, 1H, *β*′-H), 7.439 (s, 1H, *β*-H), 7.327 (s, *J* = 8.4 Hz, 1H, H-5″), 7.212 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H, H-4″), 7.166 (d, *J* = 1.2 Hz, 1H, H-3′), 7.098-7.125 (m, 2H, H-5′, H-6′), 3.874 (s, 3H, 2-OCH_3), 3.110 (s, 4H, 4′-CH_2, 5′-CH_2), 2.609-2.656 (m, 4H, -$COC\underline{H_2}CH_3$ × 2), 1.289 (t, *J* = 7.8 Hz, 6H, -$COCH_2C\underline{H_3}$ × 2). ESI-MS m/z: 435.0 $(M+1)^+$, calcd for $C_{26}H_{27}O_6$: 434.2.

2-Methoxy-4-{(E)-[(E)-3-(2-methoxybenzylidene)-2-oxocyclopentylidene]methyl}phenyl propionate (AS20): Yellow powder, 19.6% yield, mp 129.7-132.4 °C, HPLC purity (methanol: water) = 97.47. ^{1}H-NMR ($CDCl_3$) δ: 8.026 (s, 1H, H-6″), 7.543 (s, 2H, *β*-H, *β*′-H), 7.347-7.375 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.207 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-4″), 7.163 (d, *J* = 1.2 Hz, 1H, H-3), 7.093 (d, *J* = 8.4 Hz, 1H, H-6), 7.006 (t, *J* = 7.8 Hz, 1H, H-5″), 6.942 (d, *J* = 8.4 Hz, 1H, H-3″), 3.893 (s, 3H, 2″-OCH_3), 3.873 (s, 3H, 2-OCH_3), 3.068 (s, 4H, 4′-CH_2, 5′-CH_2), 2.616-2.653 (m, 2H, -$COC\underline{H_2}CH_3$), 1.288 (t, *J* = 7.8 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 393.4 $(M+1)^+$, calcd for $C_{24}H_{25}O_5$: 392.2.

2-Methoxy-4-{(E)-[(E)-2-oxo-3-(3,4,5-trimethoxybenzylidene)cyclopentylidene]methyl}phenyl propionate (AS21): Yellow powder, 8.8% yield, mp 169.9-172.4 °C, HPLC purity (methanol: water) = 91.69. ^{1}H-NMR ($CDCl_3$) δ: 7.542 (d, *J* = 15.6 Hz, 2H, *β*-H, *β*′-H), 7.212 (t, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.171 (s, 1H, H-3), 7.105 (d, *J* = 7.8 Hz, 1H, H-6), 6.849 (s, 2H, H-2″, H-6″), 3.912 (d, *J* = 2.4 Hz, 9H, 3″,4″,5″-OCH_3), 3.874 (s, 3H, 2-OCH_3), 3.129 (s, 4H, 4′-CH_2, 5′-CH_2), 2.618-2.656 (m, 2H, -$COC\underline{H_2}CH_3$), 1.284 (t, *J* = 7.8 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 452.9 $(M+1)^+$, calcd for $C_{26}H_{29}O_7$: 452.2.

4-{(E)-[(E)-3-(3-Methoxy-4-(propionyloxy)benzylidene)-2-oxocyclopentylidene]methyl}-1,2-phenylen

e dipropionate (AS22): Yellow powder, 5.2% yield, mp 159.9-162.7 °C, HPLC purity (methanol: water) = 89.46. ^{1}H-NMR ($CDCl_3$) δ: 7.557 (s, 1H, *β*′-H), 7.533 (s, 1H, *β*-H), 7.462 (t, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.432 (s, 1H, H-3), 7.275 (d, J = 8.4 Hz,1H, H-6), 7.209 (t, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-6″), 7.166 (s, 1H, H-2″), 7.104 (d, J = 7.8 Hz, 1H, H-5″), 3.874 (s, 3H, 3″-OCH_3), 3.102 (s, 4H, 4′-CH_2, 5′-CH_2), 2.572-2.655 (m, 6H, -COC$\underline{H_2}$$CH_3$ × 3), 1.262-1.301 (m, 9H, -$COCH_2C\underline{H_3}$ × 3). ESI-MS m/z: 507.2 $(M+1)^+$, calcd for $C_{29}H_{31}O_8$: 506.2.

4-{(E)-[(E)-3-(2,5-Dimethoxybenzylidene)-2-oxocyclopentylidene]methyl}-2-methoxyphenyl propionate (AS23): Yellow powder, 39.1% yield, mp 132.5-136.0 °C, HPLC purity (methanol: water) = 97.06. ^{1}H-NMR ($CDCl_3$) δ: 7.980 (s, 1H, *β*′-H), 7.542 (s, 1H, *β*-H), 7.205 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.161 (d, J = 1.8 Hz, 1H, H-3), 7.097 (t, J = 8.4 Hz, 2H, H-6, H-6″), 6.914 (dd, J_1 = 3.0 Hz, J_2 = 9.0 Hz, 1H, H-4″), 6.869 (d, J = 9.0 Hz, 1H, H-3″), 3.872 (s, 3H, 5″-OCH_3), 3.849 (s, 3H, 2″-OCH_3), 3.812 (s, 3H, 2-OCH_3), 3.076 (s, 4H, 4′-CH_2, 5′-CH_2), 2.615-2.653 (m, 2H, -COC$\underline{H_2}$$CH_3$), 1.287 (t, J = 7.8 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 423.3 $(M+1)^+$, calcd for $C_{25}H_{27}O_6$: 422.2.

4-{(E)-[(E)-3-(3,4-Dimethoxybenzylidene)-2-oxocyclopentylidene]methyl}-2-methoxyphenyl propionate (AS24): Yellow powder, 15.5% yield, mp 150.4-151.2 °C, HPLC purity (methanol: water) = 94.54. ^{1}H-NMR ($CDCl_3$) δ: 7.552 (s, 2H, *β*-H, *β*′-H), 7.238 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.213 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, H-6″), 7.170 (s, 1H, H-3), 7.136 (d, J = 1.8 Hz, 1H, H-2″), 7.099 (d, J = 7.8 Hz, 1H, H-6), 6.945 (d, J = 8.4 Hz, 1H, H-5″), 3.939 (s, 6H, 3″,4″-OCH_3), 3.906 (s, 3H, 2-OCH_3), 3.117 (s, 4H, 4′-CH_2, 5′-CH_2), 2.617-2.654 (m, 2H, -COC$\underline{H_2}$$CH_3$), 1.288 (t, J = 7.8 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 423.6 $(M+1)^+$, calcd for $C_{25}H_{27}O_6$: 422.2.

4-{(E)-[(E)-3-(2-Bromobenzylidene)-2-oxocyclopentylidene]methyl}-2-methoxyphenyl propionate (AS25): Yellow oil, 25.2% yield, HPLC purity (methanol: water) = 79.85. ^{1}H-NMR ($CDCl_3$) δ: 7.844 (s, 1H, *β*′-H), 7.664 (d, J = 8.4 Hz, 1H, H-3″), 7.581 (s, 1H, *β*-H), 7.546 (d, J = 7.8 Hz, 1H, H-5″), 7.208 (d, J

= 7.8 Hz, 2H, H-6″, H-5), 7.149 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 3H, H-4″, H-3, H-6), 3.872 (s, 3H, 2-OCH_3), 2.962-2.990 (m, 4H, 4′-CH_2, 5′-CH_2), 2.252 (q, J = 7.8 Hz, 2H, -COC$\underline{H_2}$$CH_3$), 1.288 (t, J = 7.8 Hz, 3H, -$COCH_2C\underline{H_3}$). ESI-MS m/z: 440.6 $(M+1)^+$, calcd for $C_{23}H_{21}BrO_4$: 440.1.

2-Methoxy-4-{(E)-{(E)-2-oxo-3-[4-(propionyloxy)benzylidene]cyclopentylidene}methyl}phenyl propionate (AS26): Yellow powder, 5.6% yield, mp 143.6-146.7 °C, HPLC purity (methanol: water) = 55.64. ^{1}H-NMR ($CDCl_3$) δ: 7.612 (d, J = 8.4 Hz, 2H, H-2″, H-6″), 7.569 (s, 2H, β-H, β′-H), 7.215 (d, J = 7.8 Hz, 1H, H-5), 7.177 (d, J = 8.4 Hz, 3H, H-3″, H-5″, H-6), 7.098 (d, J = 1.8 Hz, 1H, H-3), 3.876 (s, 3H, 2-OCH_3), 3.112 (s, 4H, 4′-CH_2, 5′-CH_2), 2.598-2.658 (m, 4H, -COC$\underline{H_2}$$CH_3$ × 2), 1.270-1.302 (m, 6H, -$COCH_2C\underline{H_3}$ × 2). ESI-MS m/z: 434.9 $(M+1)^+$, calcd for $C_{26}H_{27}O_6$: 434.2.

4-{(E)-[(E)-3-(4-Ethoxybenzylidene)-2-oxocyclopentylidene]methyl}-2-methoxyphenyl propionate (AS27): Yellow powder, 18.5% yield, mp 153.8-158.2 °C, HPLC purity (methanol: water) = 100.00. ^{1}H-NMR ($CDCl_3$) δ: 7.574 (d, J = 7.2 Hz, 2H, H-2″, H-6″), 7.542 (s, 2H, β-H, β′-H), 7.214 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H, H-5), 7.170 (s, 1H, H-3), 7.096 (d, J = 7.8 Hz, 1H, H-6), 6.955 (d, J = 9.0 Hz, 2H, H-3″, H-5″), 4.091 (q, J = 7.2 Hz, 2H, -OC$\underline{H_2}$$CH_3$), 3.875 (s, 3H, 2-$OCH_3$), 3.100 (s, 4H, 4′-$CH_2$, 5′-$CH_2$), 2.636 (q, J = 7.8 Hz, 2H, -OCOC$\underline{H_2}$-), 1.443 (t, J = 7.2 Hz, 3H, -$OCH_2C\underline{H_3}$), 1.289 (t, J = 7.8 Hz, 3H, -$OCOCH_2C\underline{H_3}$). ESI-MS m/z: 407.8 $(M+1)^+$, calcd for $C_{25}H_{27}O_5$: 406.2.

(3E,5E)-3-[(2-Chlorophenyl)methylidene]-1-methyl-5-[(3,4,5-trimethoxyphenyl)methylidene]piperidin-4-one (AS28): Yellow powder, 10.2% yield, mp 110.5-113.2 °C, HPLC purity (methanol: water) = 43.07. ^{1}H-NMR (d_6-DMSO) δ: 7.445 (s, 2H, β-H, β′-H), 7.371 (s, 2H, H-3″, H-6″), 7.291-7.317 (m, 2H, H-4″, H-5″), 7.261 (s, 2H, H-2′, H-6′), 3.609 (s, 9H, 3′,4′,5′-OCH_3), 2.370 (s, 4H, 2-CH_2, 6-CH_2), 1.597 (s, 3H, N-CH_3). ESI-MS m/z: 413.9 $(M+1)^+$, calcd for $C_{23}H_{25}ClNO_4$: 413.1.

(3E,5E)-3-[(2-Chlorophenyl)methylidene]-5-[(3,4-dihydroxyphenyl)methylidene]oxan-4-one (AS29): Yellow powder, 15.1% yield, mp 222.8-225.7 °C, HPLC purity (methanol: water) = 99.65. ^{1}H-NMR

(d_6-DMSO) δ: 7.775 (s, 1H, β'-H), 7.592 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H, H-3″), 7.552 (s, 1H, β-H), 7.417-7.472 (m, 2H, H-5″, H-6″), 7.313 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H, H-4″), 6.810-6.861 (m, 3H, H-2′, H-5′, H-6′), 4.887 (s, 2H, 2-CH_2), 4.759 (s, 2H, 6-CH_2). ESI-MS m/z: 343.1 $(M+1)^+$, calcd for $C_{19}H_{16}ClO_4$: 342.1.

Quantitative Structure-Activity Relationship (QSAR) Study

Descriptors calculation and selection

To obtain a QSAR model, compounds are often represented by molecular descriptors.[1] The molecular structures of all the curcumin analogs were built with Maestro (Version 9.1 Schrödinger, LLC). The full geometry optimization for the investigated molecules was carried out with MOPAC2009 version 9.0.1. All the calculations were based on the semi-empirical Parameterized model 6 (PM6) method.[2] The molecular descriptor computing was performed on MODEL (Molecular Descriptor Lab), a web-based server for computing structural and physicochemical features of compounds, according to the methods described in the literature.[3] The descriptors studied here contain the constitutional descriptors, physicochemical descriptors, topological descriptors, geometrical descriptors, charge (electronic) descriptors, and quantum chemistry descriptors. The optimized geometry of molecules was uploaded to MODEL. After the calculation of the molecular descriptors, about 4000 molecular descriptors based on molecular 3D structure were obtained. Those that stayed constant for all molecules were eliminated and pairs of variables with a correlation coefficient greater than 0.85 were classified as inter-correlated and one in each correlated pair was deleted.

Multiple linear regression (MLR) analysis

MLR analysis was a statistical technique that using several explanatory variables to predict the outcome of a response variables. The goal of multiple linear regression (MLR) is to simulation the

relationship between the explanatory and response variables. In our present study, MLR performed using R program, a powerful tool for statistical computing and graphics, to derive QSAR models. The biological data used in this study were their TNF-α- or IL-6-inhibitory rates when compared to LPS alone group. Compounds with negative values were abandoned because of their pro-inflammatory activities. The inhibition rates against TNF-α and IL-6 release, named as $IR_{TNF-\alpha}$ and IR_{IL-6} respectively, were used as dependent variables in the linearization procedure. Subsequently, Stepwise Multiple Linear Regression (Stepwise-MLR) was used to select the significant descriptors. The most relevant descriptors were used as independent variables.

Validation of the models

Validation of the lineal models is required for testing the predictive ability and generalizing the methods by cross-validation. The leave-one-out (LOO) procedure was employed. When a data point was removed from the analyzed set, the regression was recalculated, and then the predicted value for that point was compared to its actual value. This process was repeated until each datum had been omitted once and then the sum of squares of these deletion residuals could be used to calculate q^2, an equivalent statistic to R^2.

The stability analysis of curcumin, S1 and S4 by HPLC

The stability test of curcumin, **S1** and **S4** were performed using a reverse phase HPLC (Agilent Technologies 1260 Infinity, Santa Clara, CA). Briefly, 20 μL of 5 mM curcumin and its analogs (dissolved in methanol) were added to 980 μL of 0.1 M phosphate buffer (pH 7.4). Samples were incubated at 37 ^{o}C for indicated times. After incubation, 200 μL of mixtures were detected by HPLC with a mobile phase of methanol and water.

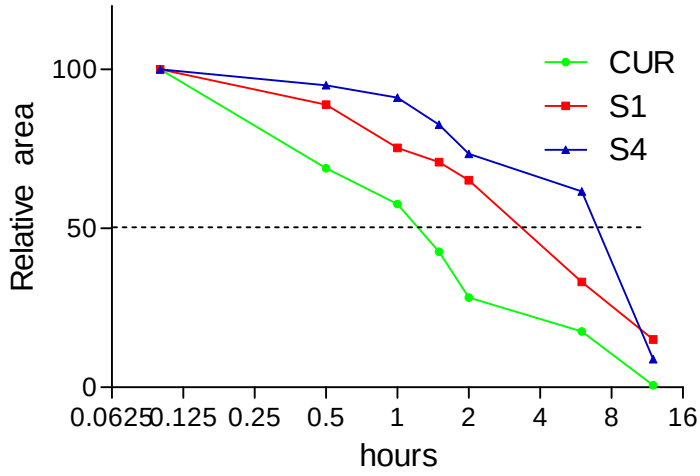

Figure S1. The stability analysis of curcumin and its analogs by HPLC.

Reference

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