

Supplementary Information

IL-6 inhibitory compounds from *Piper attenuatum* and their anticancer activities

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SI 1. Spectroscopic data of compounds 4-18

methylarctigenin (**4**): yellowish amorphous powder; C₂₂H₁₄O₄; [α]_D²⁵ -67.5 (c 0.04, CHCl₃); CD (EtOH) Δε (nm): +2.38 (211), -2.40 (232), +0.10 (285); Q-TOF-MS: *m/z* 409.1629 (Calcd for: 409.1657 [M+Na]⁺); ¹H-NMR (CDCl₃, 500 MHz): δ 6.74 (2H, dd, *J* = 9.2, 8.1 Hz, H-5,5'), 6.66 (1H, d, *J* = 2.0 Hz, H-2), 6.63 (1H, dd, *J* = 8.0, 2.0 Hz, H-6), 6.53 (1H, dd, *J* = 8.1, 2.1 Hz, H-6'), 6.46 (1H, d, *J* = 2.1 Hz, H-2'), 4.09 (1H, m, H-9'a), 3.85 (1H, m, H-9'b), 3.83 (6H, d, *J* = 2.0 Hz, 3,4-OCH₃), 3.81 (3H, s, 4'-OCH₃), 3.80 (3H, s, 3'-OCH₃), 2.92 (1H, dd, *J* = 10.6, 6.1 Hz, H-7), 2.65-2.43 (4H, m, H-7',8',8'); ¹³C-NMR (CDCl₃, 125 MHz): δ 178.9 (C-9), 149.3 (C-4), 149.2 (C-4'), 148.2 (C-3'), 148.1 (C-3), 130.7 (C-1), 130.4 (C-1'), 121.6 (C-6), 120.8 (C-6'), 112.6 (C-2), 112.1 (C-2'), 111.5 (C-5), 111.3 (C-5'), 71.4 (C-9'), 56.1-56.0 (3,4,3',4'-OCH₃), 46.8 (C-8), 41.3 (C-8'), 38.4 (C-7'), 34.7 (C-7); ESI-Q-TOF-MS: *m/z* 409.1629 (Calcd for: 409.1657 [M+Na]⁺).

(-)kusunokininin (**5**): yellowish amorphous powder; C₂₁H₂₂O₆; [α]_D²⁵ -46.1 (c 0.17, CHCl₃); CD (MeOH) Δε (nm): -3.38 (234), -0.20 (287); ¹H-NMR (CDCl₃, 500 MHz): δ 6.74 (1H, d, *J* = 8.0 Hz, H-5'), 6.69 (1H, d, *J* = 8.0 Hz, H-5), 6.58 (1H, brd, *J* = 2.0 Hz, H-2), 6.56 (1H, m, H-6'), 6.54 (1H, dd, *J* = 8.0, 2.0 Hz, H-6), 6.46 (1H, d, *J* = 2.0 Hz, H-2'), 5.91 (2H, dd, *J* = 5.0, 1.3 Hz, -OCH₂O), 4.13 (1H, dd, *J* = 9.1, 7.0 Hz, H-9'a), 3.86 (1H, m, H-9'b), 3.83 (3H, s, 3'-OCH₃), 3.80 (3H, s, 4'-OCH₃), 2.94 (1H, dd, *J* = 14.1, 5.2 Hz, H-7a), 2.83 (1H, dd, *J* = 14.1, 7.1 Hz, H-7b), 2.62-2.42 (4H, m, H-7'a,7'b,8',8'); ¹³C-NMR (CDCl₃, 125 MHz): δ 178.7 (C-9), 149.3 (C-3'), 148.1 (C-4'), 148.0 (C-3), 146.7 (C-4), 131.6 (C-1), 130.6 (C-1'), 122.6 (C-6), 120.9 (C-6'), 111.9 (C-2'), 111.6 (C-5'), 109.7 (C-2), 108.4 (C-5), 101.3 (-OCH₂O), 71.4 (C-9), 56.1 (4'-OCH₃), 56.0 (3'-OCH₃), 46.7 (C-8), 41.4 (C-8'), 38.5 (C-7'), 35.0 (C-7); ESI-Q-TOF-MS: *m/z* 393.1324 (Calcd for: 393.1314 [M+Na]⁺).

(-)haplomyrfozin (**6**): yellowish amorphous powder; C₂₀H₂₀O₆; [α]_D²⁵ -68.5 (c 0.08, MeOH); CD (MeOH) Δε (nm): -1.14 (233); ¹H-NMR (CDCl₃, 500 MHz): δ 6.79 (1H, d, *J* = 8.0 Hz, H-5'), 6.70 (1H, d, *J* = 8.0 Hz, H-5), 6.59 (1H, d, *J* = 1.5 Hz, H-2), 6.57 (1H, dd, *J* = 8.0, 1.5 Hz, H-6), 6.50 (1H, dd, *J* = 8.0, 1.6 Hz, H-6'), 6.44 (1H, d, *J* = 1.6 Hz, H-2'), 5.91 (2H, dd, *J* = 3.5, 1.4 Hz, -OCH₂O), 4.12 (1H, dd, *J* = 9.0, 1.2 Hz, H-9'a), 3.85 (1H, dd, *J* = 9.0, 7.4 Hz, H-9'b), 3.83 (3H, s, 3'-OCH₃), 2.94 (1H, dd, *J* = 14.1, 5.1 Hz, H-7a), 2.83 (1H, dd, *J* = 14.1, 7.1 Hz, H-7b), 2.57 (1H, dd, *J* = 12.4, 5.0 Hz, H-7'a), 2.53 (1H, d, *J* = 6.0 Hz, H-8), 2.46 (1H, brd, *J* = 12.4 Hz, H-7'b), 2.45 (1H, dd, *J* = 10.0, 5.5 Hz, H-8'); ¹³C-NMR (CDCl₃, 125 MHz): δ 178.7 (C-9), 148.2 (C-3), 146.8 (C-4), 146.7 (C-3'), 144.7 (C-4'), 131.6 (C-1), 130.0 (C-1'), 122.5 (C-6), 121.5 (C-6'), 114.7 (C-5'), 111.2 (C-2'), 109.7 (C-2), 108.4 (C-5), 101.2 (-OCH₂O), 71.4 (C-9'), 56.1 (3'-OCH₃), 46.7 (C-8), 41.5 (C-8'), 37.6 (C-7'), 35.0 (C-7); ESI-Q-TOF-MS: *m/z* 379.1162 (Calcd for: 379.1158 [M+Na]⁺).

piperdardine (**7**): yellowish amorphous powder; C₁₉H₂₃NO₃; ¹H-NMR (CDCl₃, 500 MHz): δ 7.19 (1H, dd, *J* = 14.8, 10.8 Hz, H-3'), 6.69 (1H, d, *J* = 7.9 Hz, H-5''), 6.63 (1H, d, *J* = 1.6 Hz, H-2''), 6.58 (1H, dd, *J* = 7.9, 1.6 Hz, H-6''), 6.23 (1H, d, *J* = 14.8 Hz, H-2'), 6.16 (1H, dd, *J* = 15.3, 10.8 Hz, H-4'), 6.03 (1H, dt, *J* = 15.3, 7.4 Hz, H-5'), 5.89 (2H, s, -OCH₂O), 3.58 (2H, brs, H-6), 3.45 (2H, brs, H-2), 2.63 (2H, t, *J* = 8.7, 6.6 Hz, H-7'), 2.39 (2H, q, *J* = 7.4 Hz, H-6'), 1.65-1.58 (2H, m, H-4), 1.56-1.50 (4H, m, H-3,5); ¹³C-NMR (CDCl₃, 125 MHz): δ 165.8 (C-1'), 147.8 (C-3''), 145.9 (C-4''), 142.7 (C-3'), 141.1 (C-5'), 135.4 (C-1''), 129.7 (C-4'), 121.4 (C-6''), 119.3 (C-2'), 109.0 (C-2''), 108.8 (C-5''), 101.0 (-OCH₂O), 47.1 (C-6), 43.4 (C-2),

35.19 (C-6'), 35.16 (C-7'), 26.9 (C-5), 25.8 (C-3), 24.9 (C-4); ESI-Q-TOF-MS: *m/z* 314.1766 (Calcd for: 314.1756 [M+H]⁺).

piperine (**8**): yellowish amorphous powder; C₁₇H₁₉NO₃; ¹H-NMR (CDCl₃, 500 MHz): δ 7.38 (1H, ddd, *J* = 14.7, 8.8, 1.4 Hz, H-3'), 6.96 (1H, d, *J* = 1.7 Hz, H-2"), 6.87 (1H, dd, *J* = 8.1, 1.7 Hz, H-6"), 6.76 (1H, dd, *J* = 8.1 Hz, H-5"), 6.72 (2H, m, H-4',5'), 6.42 (1H, d, *J* = 14.7 Hz, H-2'), 5.95 (2H, s, -OCH₂O), 3.61 (2H, s, H-2), 3.50 (2H, s, H-6), 1.64 (2H, dt, *J* = 10.6, 3.5 Hz, H-4), 1.61-1.53 (4H, m, H-3,5) ; ¹³C-NMR (CDCl₃, 125 MHz): δ 165.6 (C-1'), 148.4 (C-3"), 148.3 (C-4"), 142.7 (C-3'), 138.3 (C-5'), 131.3 (C-1"), 125.6 (C-4'), 122.7 (C-6"), 120.3 (C-2'), 108.7 (C-5"), 105.9 (C-2"), 101.4 (-OCH₂O), 47.1 (C-6), 43.5 (C-2), 27.0 (C-5), 25.8 (C-3), 24.9 (C-4); ESI-Q-TOF-MS: *m/z* 286.1453 (Calcd for: 286.1443 [M+H]⁺).

piperanine (**9**): yellowish amorphous powder; C₁₇H₁₉NO₃; ¹H-NMR (CDCl₃, 500 MHz): δ 6.77 (1H, dt, *J* = 15.0, 7.0 Hz, H-3'), 6.70 (1H, d, *J* = 7.9 Hz, H-5"), 6.65 (1H, d, *J* = 1.4 Hz, H-2"), 6.60 (1H, dd, *J* = 7.9, 1.4 Hz, H-6"), 6.19 (1H, d, *J* = 15.0 Hz, H-2'), 5.89 (2H, s, -OCH₂O), 3.56 (2H, brs, H-2), 3.39 (2H, brs, H-6), 2.67 (2H, t, *J* = 7.4 Hz, H-5'), 2.44 (2H, q, *J* = 7.4 Hz, H-4'), 1.62 (2H, dt, *J* = 11.2, 5.6 Hz, H-4), 1.52 (4H, brs, H-3,5); ¹³C-NMR (CDCl₃, 125 MHz): δ 165.7 (C-1'), 147.8 (C-3"), 146.0 (C-4"), 144.2 (C-3'), 135.2 (C-1"), 121.6 (C-2'), 121.4 (C-6"), 109.1 (C-2"), 108.4 (C-5"), 101.0 (-OCH₂O), 47.1 (C-6), 43.3 (C-2), 34.8 (C-4'), 34.7 (C-5'), 26.8 (C-5), 25.8 (C-3), 24.8 (C-4); ESI-Q-TOF-MS: *m/z* 288.1597 (Calcd for: 288.1600 [M+H]⁺).

guineensine (**10**): yellowish amorphous powder; C₁₇H₁₉NO₃; ¹H-NMR (CDCl₃, 500 MHz): δ 7.17 (1H, dd, *J* = 15.0, 10.3 Hz, H-3), 6.87 (1H, d, *J* = 1.4 Hz, H-2'), 6.73 (1H, dd, *J* = 7.9, 1.4 Hz, H-6'), 6.71 (1H, dd, *J* = 7.9 Hz, H-5'), 6.26 (1H, d, *J* = 15.7 Hz, H-13), 6.04 (2H, m, H-4,5), 6.02 (1H, d, *J* = 15.7 Hz, H-12), 5.90 (2H, s, -OCH₂O), 5.73 (1H, d, *J* = 15.0 Hz, H-2), 3.14 (2H, t, *J* = 6.6 Hz, H-1"), 2.13 (4H, m, H-6,11), 1.78 (1H, dt, *J* = 13.4, 6.6 Hz, H-2"), 1.40 (4H, m, H-7,10), 1.30 (4H, m, H-8,9), 0.91 (3H, s, H-4"), 0.89 (3H, s, H-3"); ¹³C-NMR (CDCl₃, 125 MHz): δ 166.6 (C-1), 148.1 (C-3'), 146.7 (C-4'), 143.3 (C-5), 141.5 (C-3), 132.7 (C-1'), 129.6 (C-13), 129.5 (C-12), 128.5 (C-4), 122.0 (C-2), 120.4 (C-6'), 108.4 (C-5'), 105.6 (C-2'), 101.1 (-OCH₂O), 47.2 (C-1"), 33.1 (C-11), 33.0 (C-6), 29.6 (C-10), 29.2 (C-8), 29.1 (C-9), 28.9 (C-7), 28.8 (C-2"), 20.3 (C-3",4"); ESI-Q-TOF-MS: *m/z* 406.2369 (Calcd for: 406.2358 [M+H]⁺).

(6*S*)-dehydromifolol (**11**): white amorphous powder; C₁₃H₁₈O₃; [α]²⁸_D +175 (*c* 0.03, MeOH); CD (MeOH) Δε (nm): +24.8 (258), -4.66 (322); ¹H-NMR (CD₃OD, 500 MHz): δ 6.92 (1H, d, *J* = 15.8 Hz, H-7), 6.37 (1H, d, *J* = 15.8 Hz, H-8), 5.87 (1H, m, *J* = 1.4 Hz, H-4), 2.53 (1H, d, *J* = 17.1 Hz, H-2a), 2.21 (1H, d, *J* = 17.1 Hz, H-2b), 2.24 (3H, s, H-10), 1.84 (3H, d, *J* = 1.4 Hz, H-13), 0.99 (3H, s, H-11), 0.95 (3H, s, H-12); ¹³C-NMR (CD₃OD, 125 MHz) δ 200.8 (C-9), 200.5 (C-3), 164.8 (C-5), 148.5 (C-7), 131.9 (C-8), 128.2 (C-4), 80.1 (C-6), 50.7 (C-2), 42.8 (C-1), 27.8 (C-10), 24.9 (C-12), 23.7 (C-11), 19.3 (C-13); ESI-Q-TOF-MS: *m/z* 245.1158 (Calcd for: 245.1154 [M+Na]⁺).

(-)-loliolide (**12**): white amorphous powder; C₁₁H₁₆O₃; [α]²⁵_D -36.8 (*c* 0.05, CHCl₃); CD (MeOH) Δε (nm): +1.75 (213), -14.82 (229); ¹H-NMR (CD₃OD, 500 MHz): δ 5.75 (1H, s, H-7), 4.21 (1H, p, *J* = 3.6 Hz, H-3), 2.42 (1H, dt, *J* = 13.3, 2.5 Hz, H-4a), 1.99 (1H, m, H-2a), 1.76 (3H, s, H-11), 1.74 (1H, d, *J* = 4.0 Hz, H-4b), 1.53 (1H, dd, *J* = 14.5, 3.6 Hz, H-2b), 1.47 (3H, s, H-9), 1.28 (3H, s, H-10); ¹³C-NMR (CD₃OD, 125 MHz): δ 185.9 (C-6), 174.6 (C-8), 113.5 (C-7), 89.1 (C-5), 67.4 (C-3), 48.1 (C-2), 46.6 (C-4), 37.3 (C-1), 31.2 (C-10), 27.6 (C-11), 27.1 (C-9); ESI-Q-TOF-MS: *m/z* 219.0998 (Calcd for: 219.0997 [M+Na]⁺).

piperolactam A (**13**): white amorphous powder; C₁₆H₁₁NO₃; ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 10.65 (1H, brs, -NH), 9.27 (1H, d, *J* = 6.1 Hz, H-5), 7.93 (1H, m, H-8), 7.76 (1H, s, H-2), 7.55 (1H, m, H-6), 7.54 (1H, m, H-7), 7.12 (1H, s, H-9), 4.05 (3H, s, 3-OCH₃); ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ 168.9 (C=O), 149.4 (C-3), 148.2 (C-4), 135.2 (C-10), 134.1 (C-5a), 128.7 (C-8), 127.4 (C-5), 126.7 (C-9a), 126.6 (C-6), 124.9 (C-7), 124.3 (C-10a), 115.9 (C-1), 114.4 (C-4a), 108.5 (C-2), 104.3 (C-9), 57.2 (3-OCH₃); ESI-Q-TOF-MS: *m/z* 288.0632 (Calcd for: 288.0637 [M+Na]⁺).

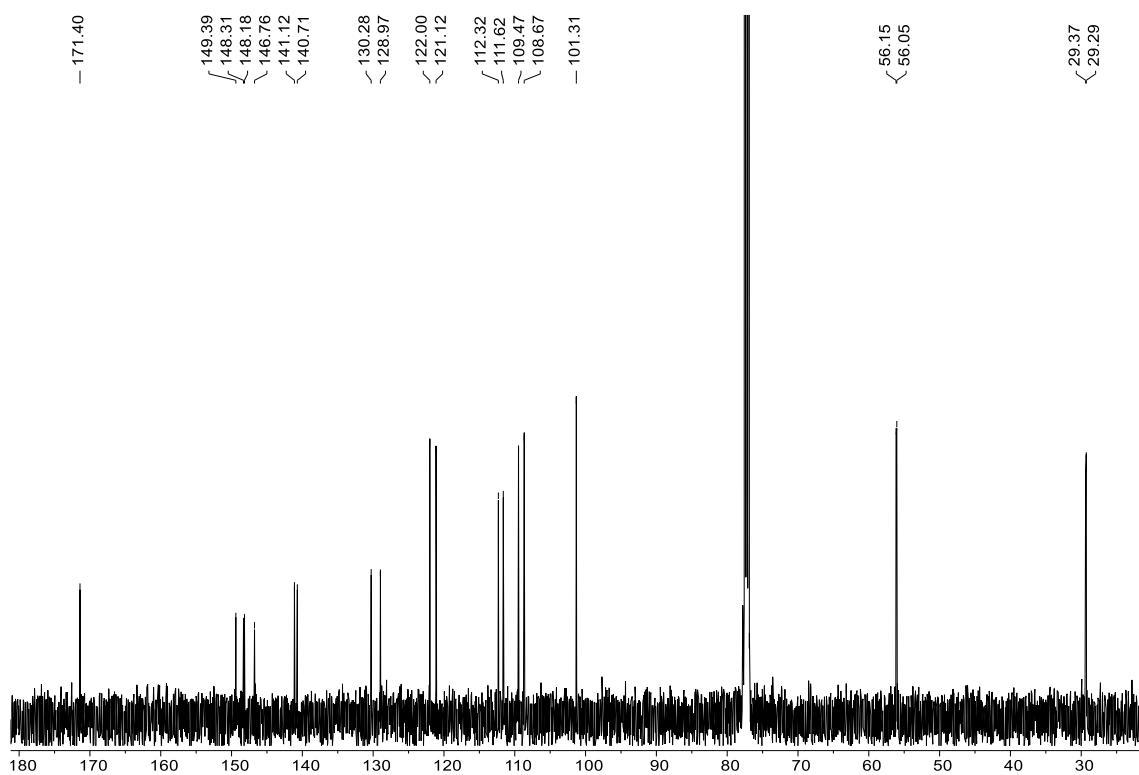
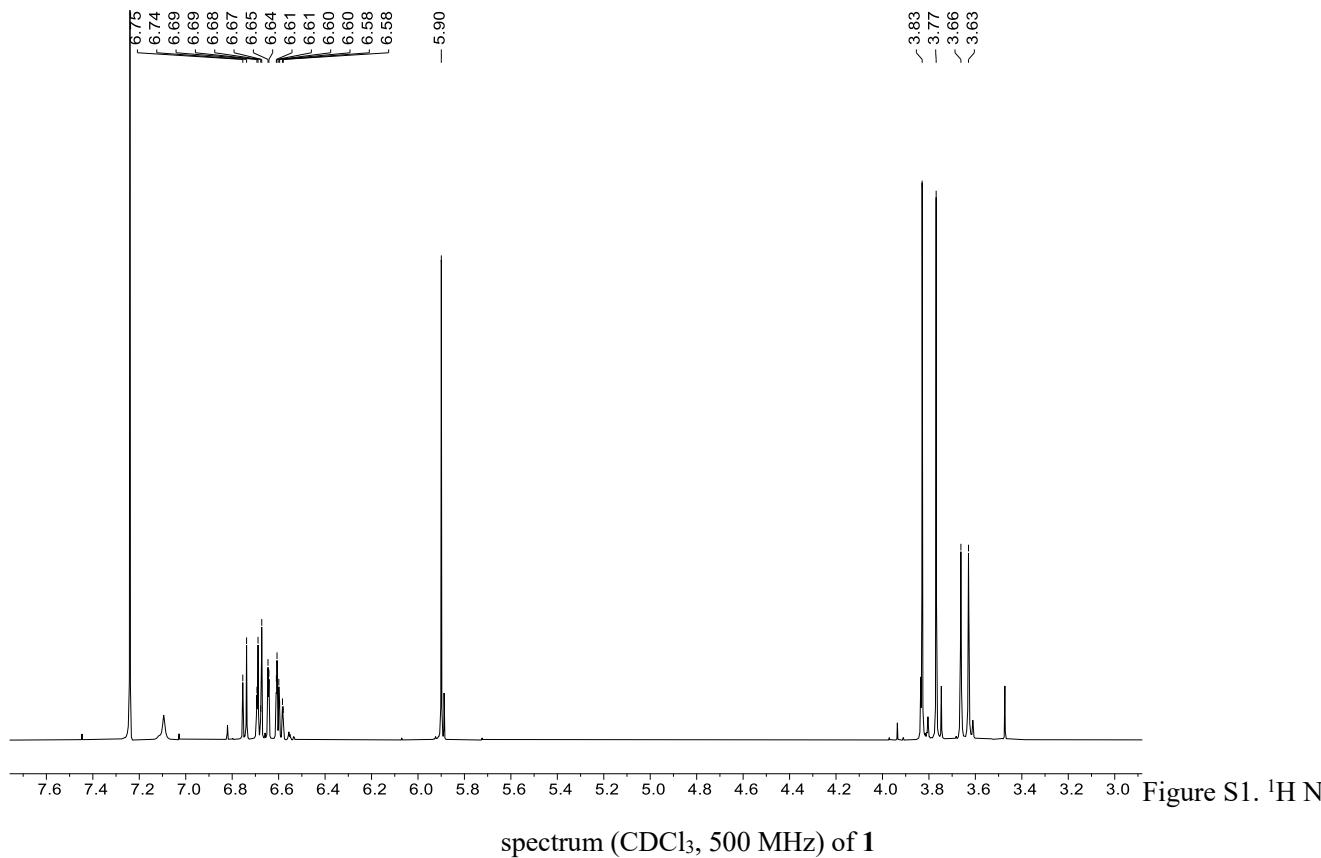
aristolactam BII (**14**): pale yellow needles; C₁₇H₁₃NO₃; ¹H-NMR (CDCl₃, 500 MHz): δ 9.18 (1H, d, *J* = 8.0 Hz, H-5), 7.82 (1H, m, H-8), 7.64 (2H, m, H-6,7), 7.38 (1H, s, H-2), 7.18 (1H, s, H-9), 4.52 (3H, s, 3-OCH₃), 4.05 (3H, s, 4-OCH₃); ¹³C-NMR (CDCl₃, 125 MHz): δ 153.2 (C-3), 110.5 (C-1), 64.0 (3-OCH₃), 62.7 (4-OCH₃); ESI-Q-TOF-MS: *m/z* 278.1479 (Calcd for: 278.0817 [M+H]⁺).

p-hydroxybenzoic acid (**15**): white solid; C₇H₆O₃; ¹H-NMR (CD₃OD, 500 MHz): δ 7.87 (2H, d, *J* = 8.7 Hz, H-2,6), 6.81 (2H, d, *J* = 8.7 Hz, H-3,5); ¹³C-NMR (CD₃OD, 125 MHz): δ 170.3 (C-7), 163.5 (C-4), 133.2 (C-2,6), 123.0 (C-1), 116.2 (C-3,5); ESI-Q-TOF-MS: *m/z* 139.0392 (Calcd for: 139.0395 [M+H]⁺).

vitexin (**16**): yellowish amorphous powder; C₂₁H₂₀O₁₀; ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 13.17 (1H, s, 5-OH), 10.86 (1H, s, 7-OH), 10.37 (1H, s, 4'-OH), 8.03 (2H, d, *J* = 8.8 Hz, H-2',6'), 6.89 (1H, d, *J* = 8.8 Hz, H-3',5'), 6.79 (1H, s, H-3), 6.27 (1H, s, H-6), 4.68 (1H, d, *J* = 9.9 Hz, H-1"), 3.83 (1H, m, H-2"), 3.76 (1H, dd, *J* = 11.4, 6.0 Hz, H-6'a), 3.52 (1H, dt, *J* = 11.4, 5.6 Hz, H-6'b), 3.38 (1H, dd, *J* = 9.6, 5.0 Hz, H-4"), 3.24 (2H, m, H-3",5"); ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ 183.1 (C-4), 164.1 (C-2), 163.6 (C-5), 162.4 (C-7), 161.1 (C-4'), 156.0 (C-9), 129.1 (C-2',6'), 121.4 (C-1'), 115.9 (C-3',5'), 104.4 (C-8), 104.0 (C-10), 101.8 (C-3), 97.5 (C-6), 81.7 (C-5"), 78.3 (C-3"), 73.2 (C-1"), 70.2 (C-2",4"), 60.8 (C-6"); ESI-Q-TOF-MS: *m/z* 433.1121 (Calcd for: 433.1135 [M+H]⁺).

ficuflavoside (**17**): yellowish amorphous powder; C₂₆H₂₈O₁₄; ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 13.17 (1H, s, 5-OH), 10.94 (1H, s, 7-OH), 10.37 (1H, s, 4'-OH), 8.04 (2H, d, *J* = 8.9 Hz, H-2',6'), 6.89 (2H, d, *J* = 8.9 Hz, H-3',5'), 6.78 (1H, s, H-3), 6.27 (1H, s, H-6), 5.00 (1H, d, *J* = 1.1 Hz, H-1""), 4.72 (1H, d, *J* = 10.0 Hz, H-1"), 4.02 (1H, dd, *J* = 10.0, 8.5 Hz, H-2"), 3.77 (1H, m, H-6'a), 3.54 (1H, dd, *J* = 5.5, 1.1 Hz, H-2""), 3.52 (1H, m, H-6'b), 3.41 (2H, m, H-3",4"), 3.23 (1H, m, H-5"), 3.13 (1H, m, H-4""a), 3.03 (1H, dd, *J* = 11.4, 5.5 Hz, H-4""b), 2.94 (1H, d, *J* = 9.2 Hz, H-5""a), 2.26 (1H, d, *J* = 9.2 Hz, H-5""b); ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ 182.0 (C-4), 163.9 (C-2), 162.7 (C-5), 161.3 (C-7), 160.5 (C-4'), 155.3 (C-9), 129.0 (C-2',6'), 121.6 (C-1'), 115.8 (C-3',5'), 109.3 (C-1""), 104.2 (C-8), 103.9 (C-10), 102.4 (C-3), 98.1 (C-6), 81.75 (C-5"), 79.07 (C-3"), 79.04 (C-3""), 75.5 (C-2""), 74.8 (C-2"), 73.2 (C-5""), 71.7 (C-1"), 70.7 (C-4"), 64.2 (C-4""), 61.1 (C-6"); ESI-Q-TOF-MS: *m/z* 565.1543 (Calcd for: 565.1557 [M+H]⁺).

vitexin 2"-*O*-β-D-glucopyranoside (**18**): yellowish amorphous powder; C₂₇H₃₀O₁₅; ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 13.15 (1H, s, 5-OH), 8.00 (2H, d, *J* = 8.8 Hz, H-2',6'), 6.89 (2H, d, *J* = 8.8 Hz, H-3',5'), 6.74 (1H, s, H-3), 6.22 (1H, s, H-6), 4.80 (1H, d, *J* = 10.0 Hz, H-1"), 3.92 (1H, d, *J* = 7.8 Hz, H-1"); ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ 164.1 (C-2), 161.5 (C-4'), 160.7 (C-5), 156.4 (C-9), 128.0 (C-2',6'), 121.3 (C-1'), 115.4 (C-3',5'), 104.78 (C-1""), 103.5 (C-8), 103.5 (C-10), 102.2 (C-3), 97.5 (C-6), 81.3 (C-5"), 80.9 (C-2"), 77.9 (C-3"), 75.8 (C-5""), 75.8 (C-3""), 73.6 (C-2""), 71.1 (C-1"), 69.4 (C-4"), 68.9 (C-4""), 60.8 (C-6"), 60.0 (C-6""), ND (C-7, C-8, C-4) (ND=Not Detected); ESI-Q-TOF-MS: *m/z* 593.1531 (Calcd for: 593.1506 [M+Na]⁺).



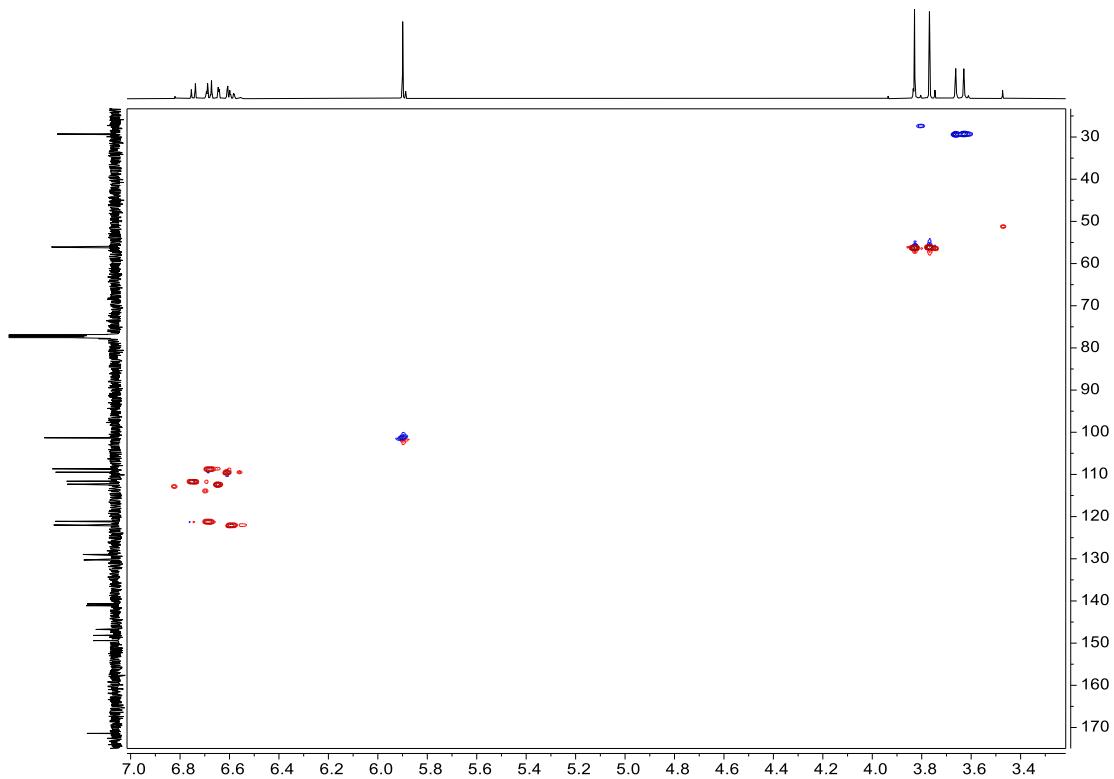


Figure S3. HSQC spectrum of **1**

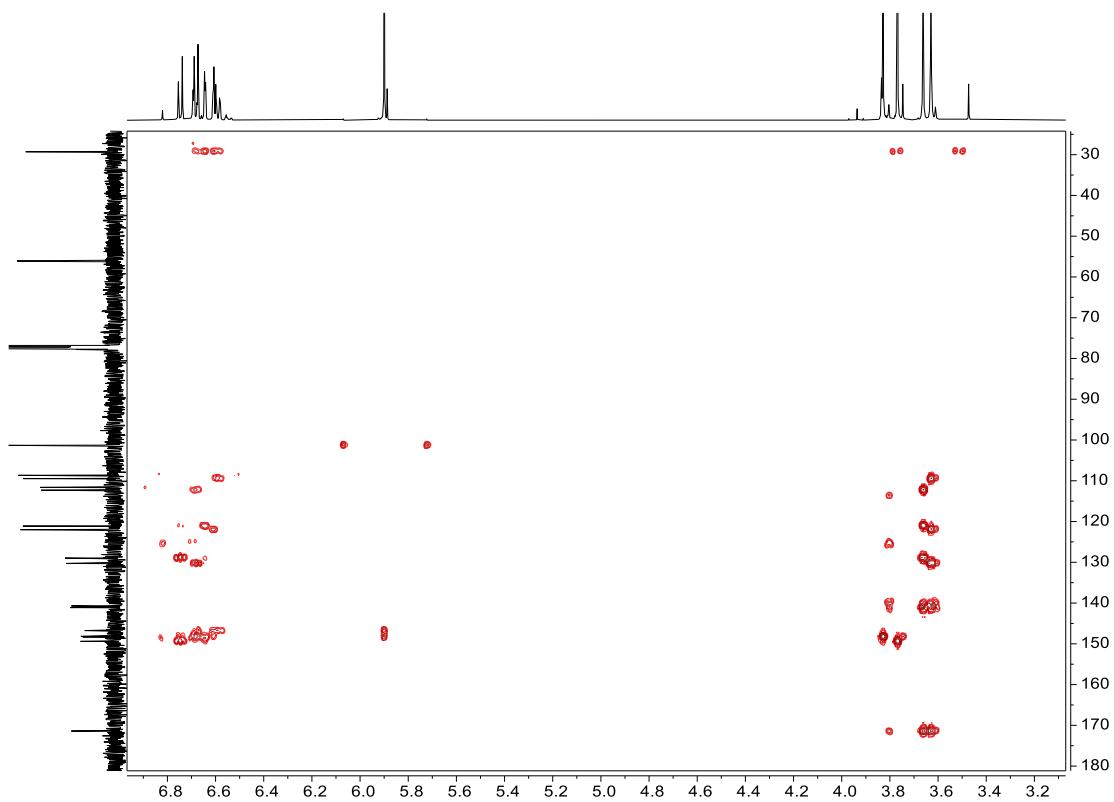


Figure S4. HMBC spectrum of **1**

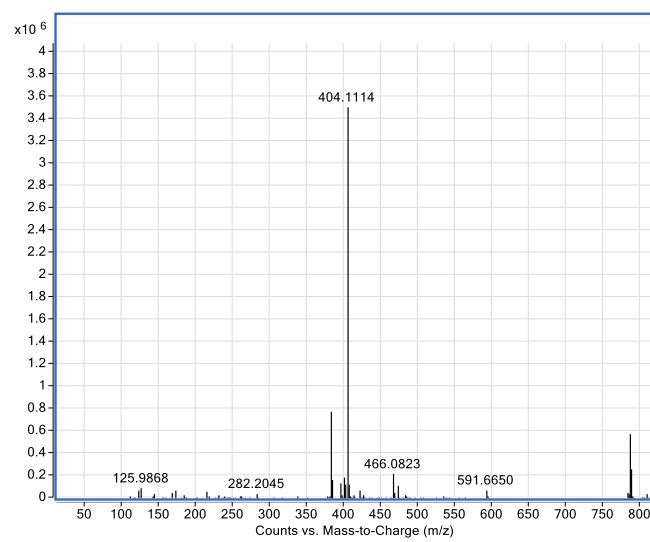


Figure S5. ESI-Q-TOF-MS spectrum of **1**

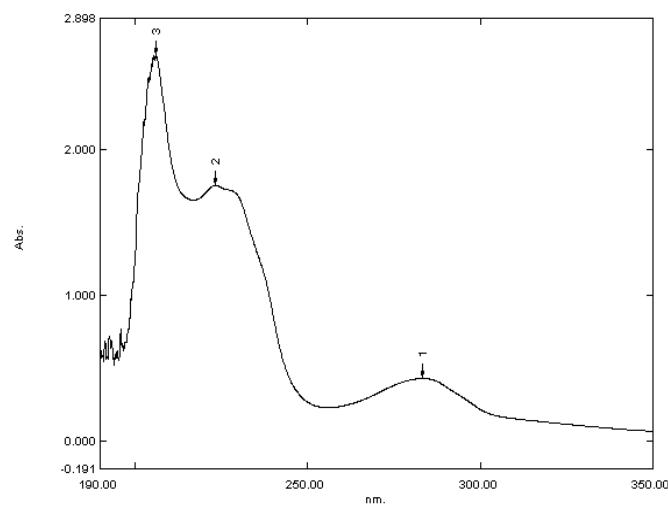


Figure S6. UV spectrum of **1**

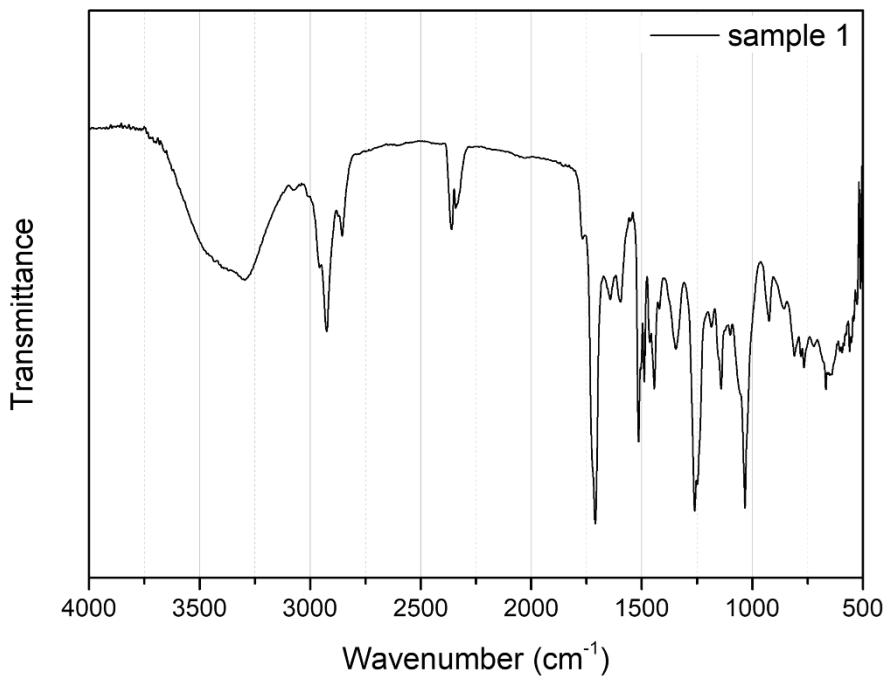


Figure S7. IR spectrum of **1**

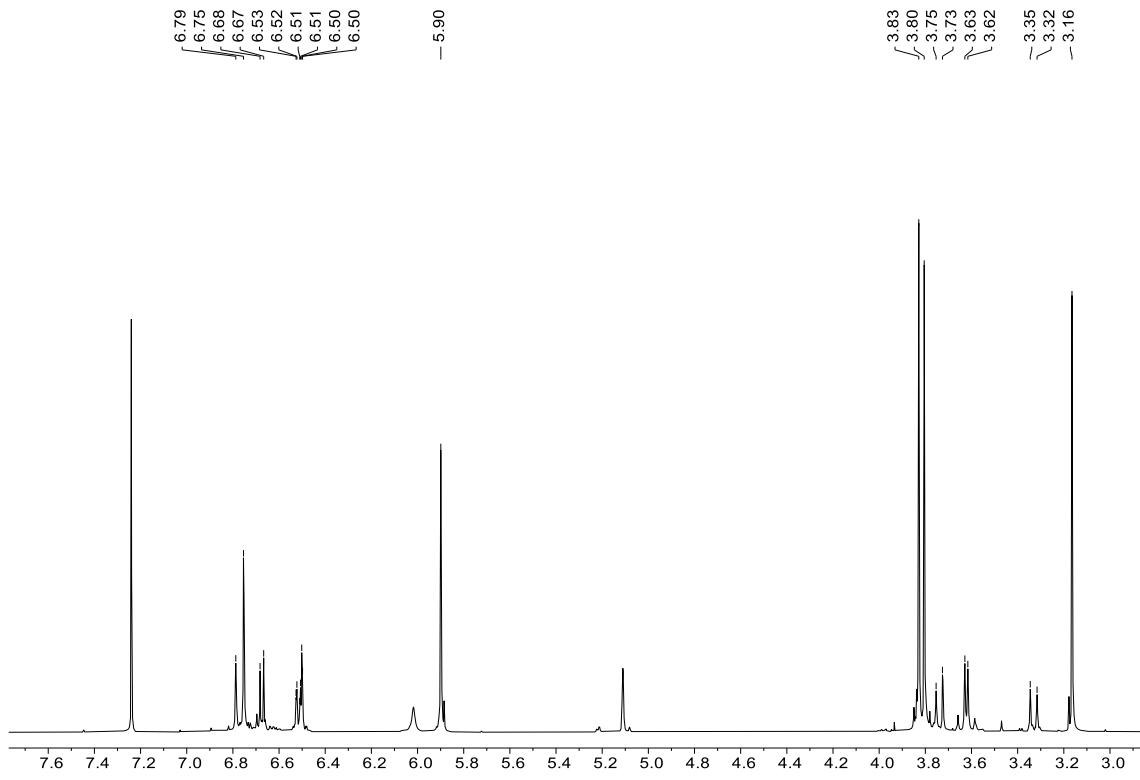


Figure S8. ^1H NMR spectrum (CDCl_3 , 500 MHz) of **2**

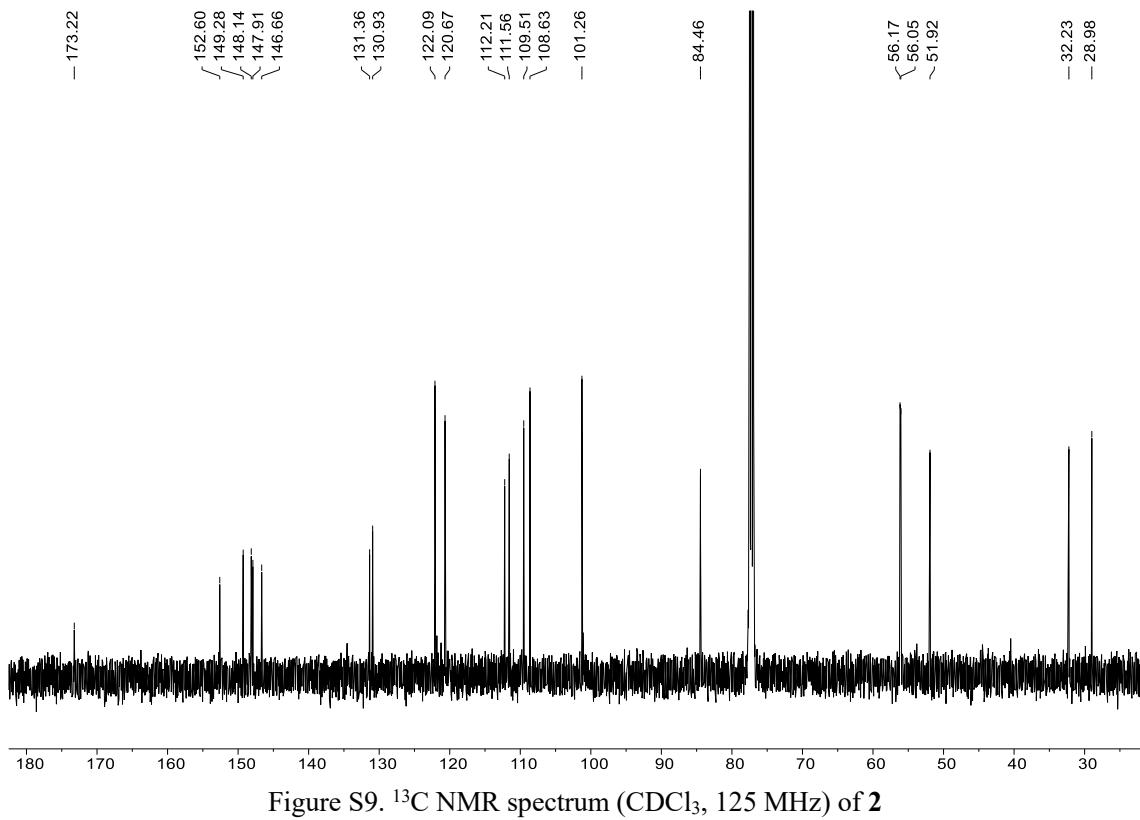


Figure S9. ^{13}C NMR spectrum (CDCl_3 , 125 MHz) of **2**

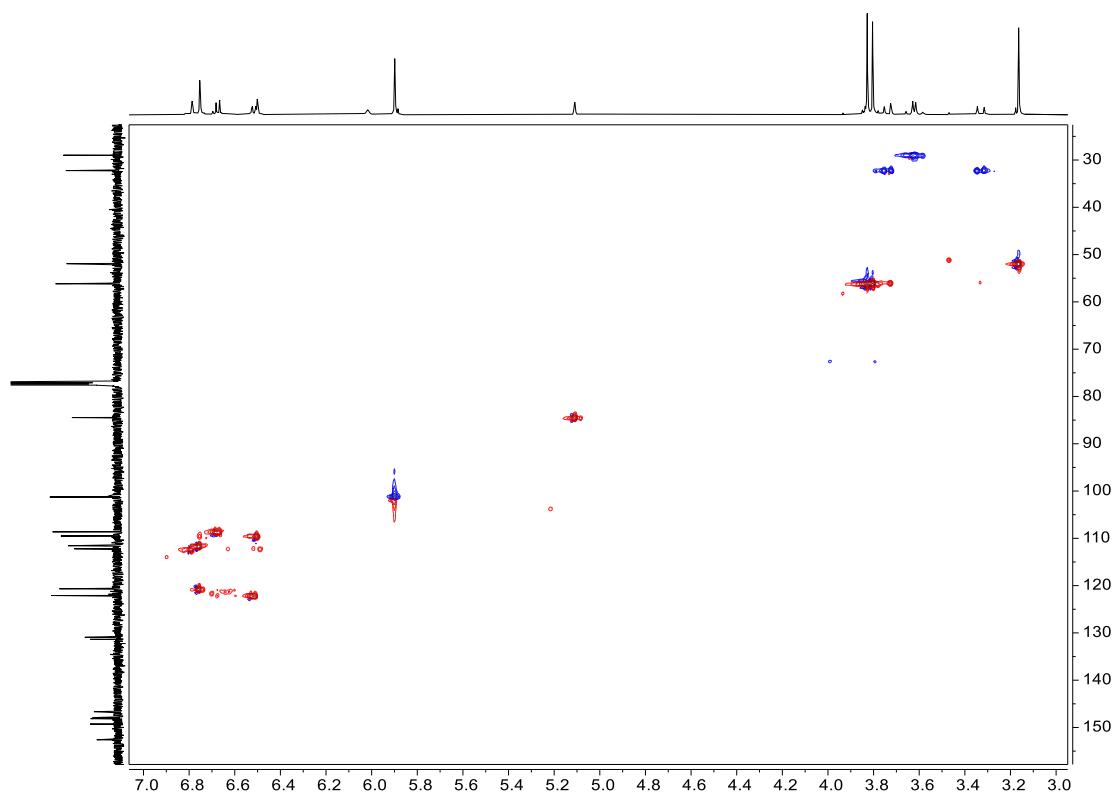


Figure S10. HSQC spectrum of **2**

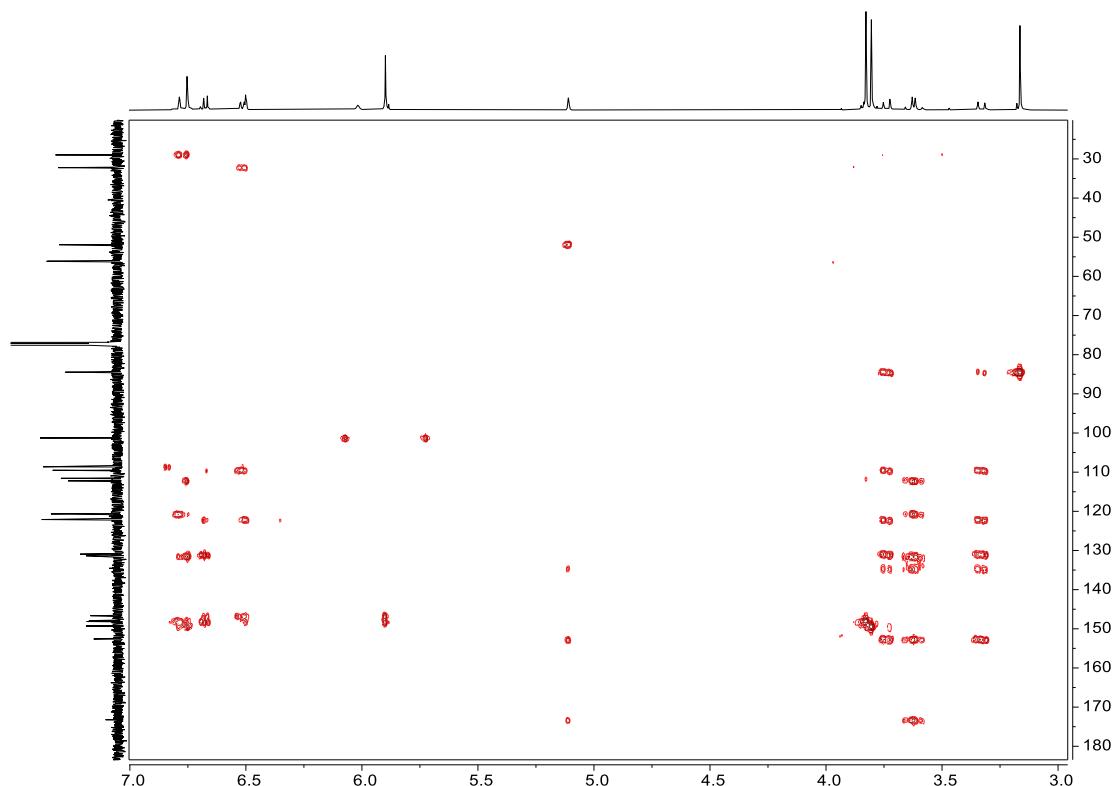


Figure S11. HMBC spectrum of **2**

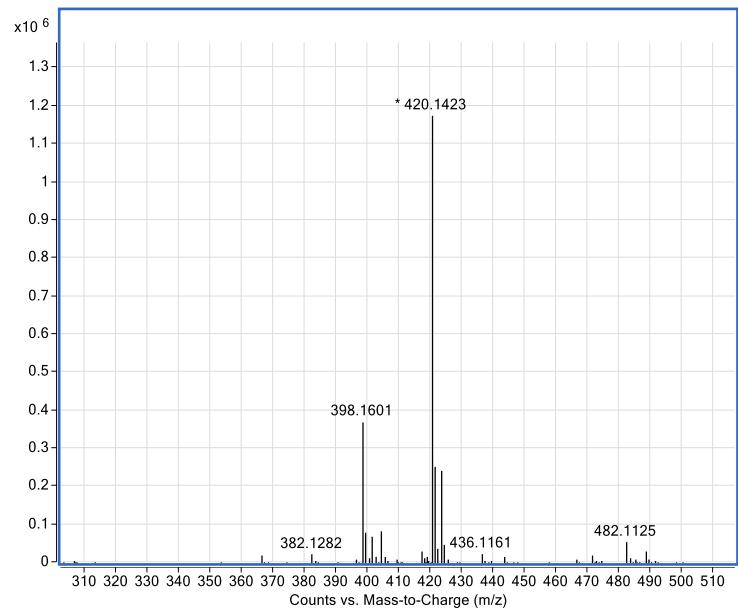


Figure S12. ESI-Q-TOF-MS spectrum of **2**

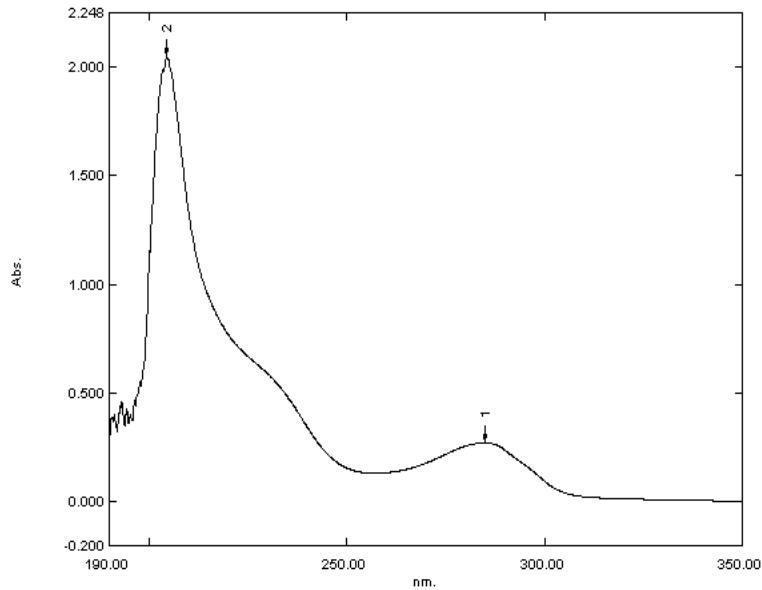


Figure S13. UV spectrum of **2**

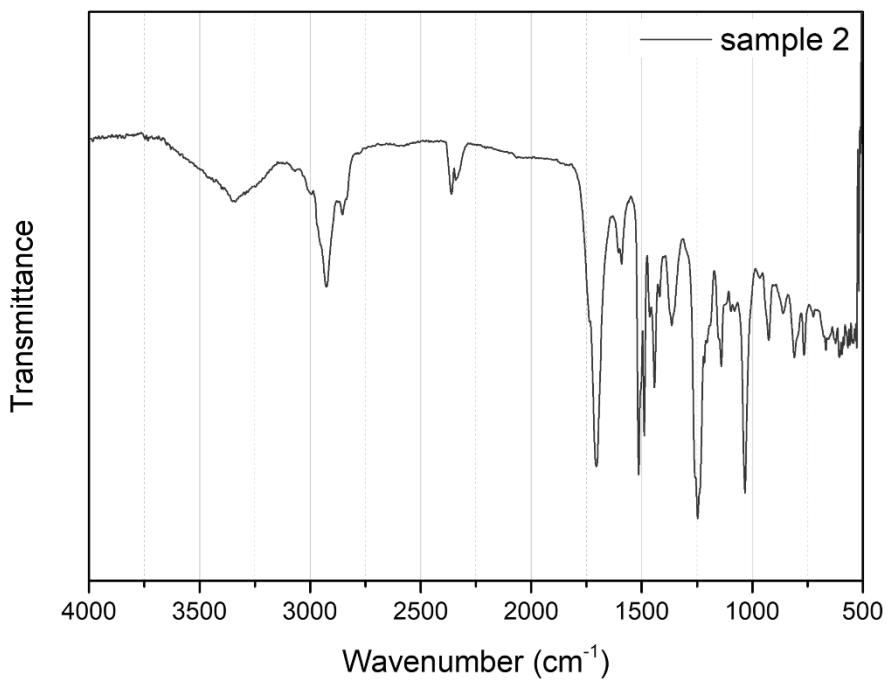


Figure S14. IR spectrum of **2**

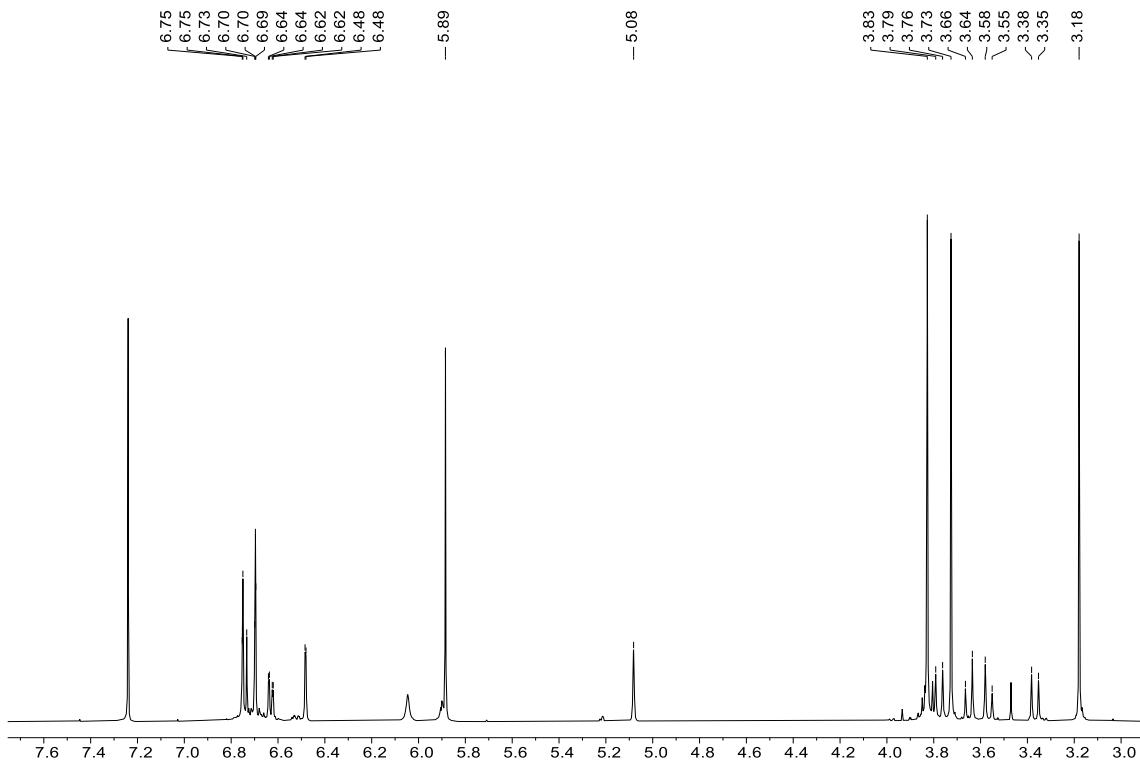


Figure S15. ^1H NMR spectrum (CDCl_3 , 500 MHz) of **3**

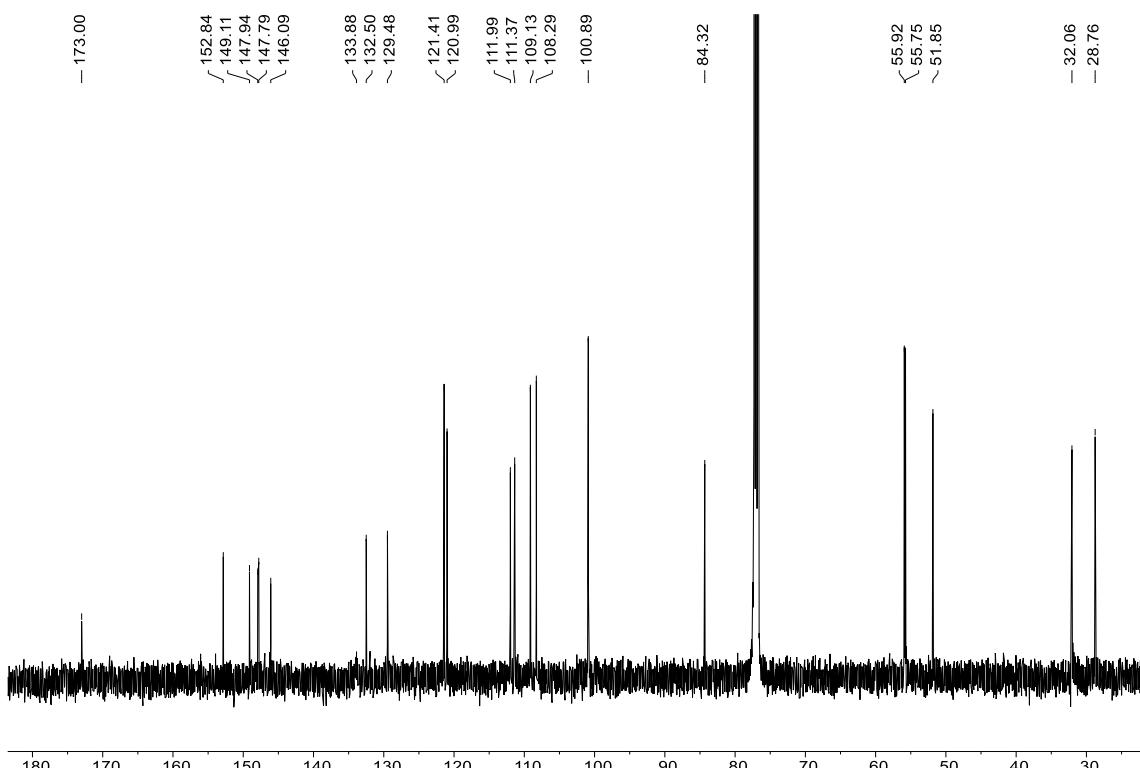


Figure S16. ^{13}C NMR spectrum (CDCl_3 , 125 MHz) of **3**

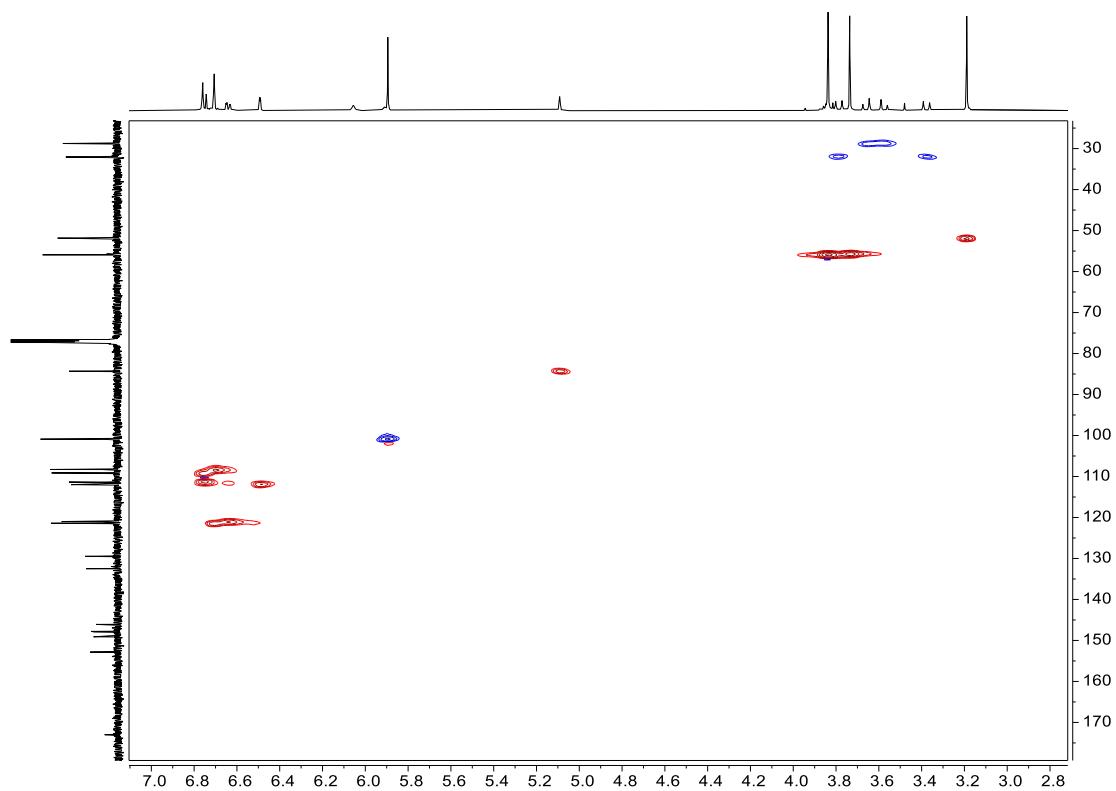


Figure S17. HSQC spectrum of **3**

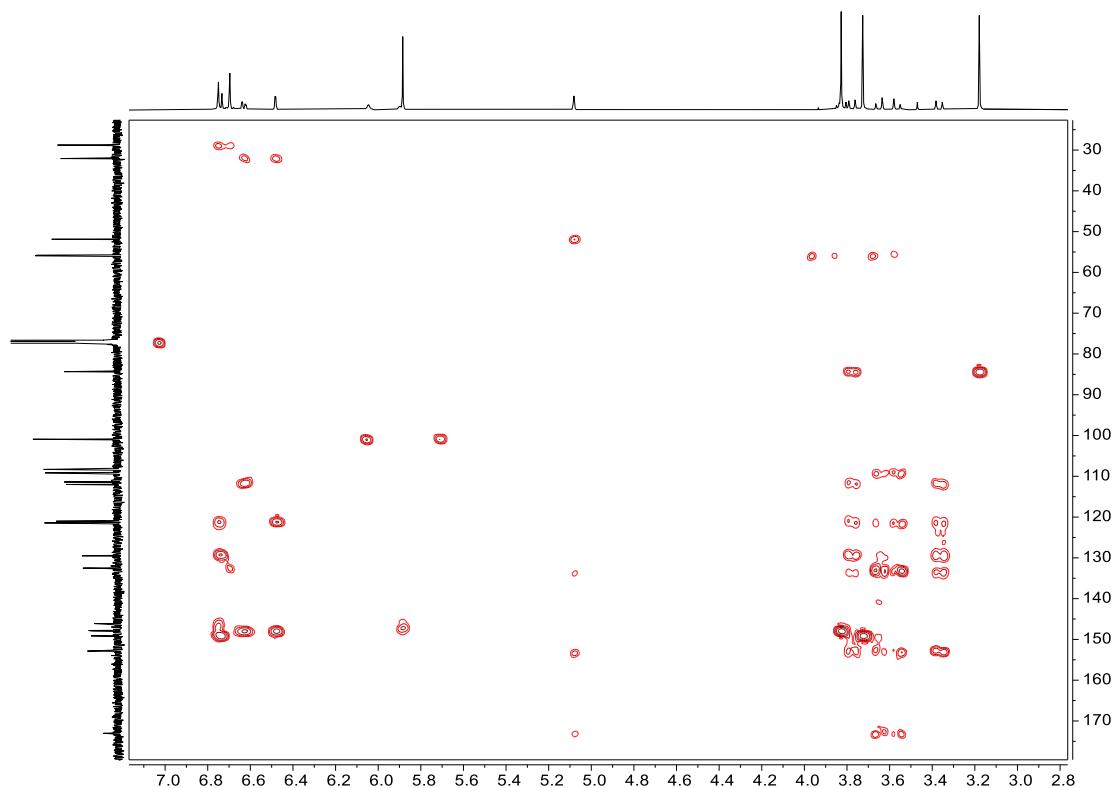


Figure S18. HMBC spectrum of **3**

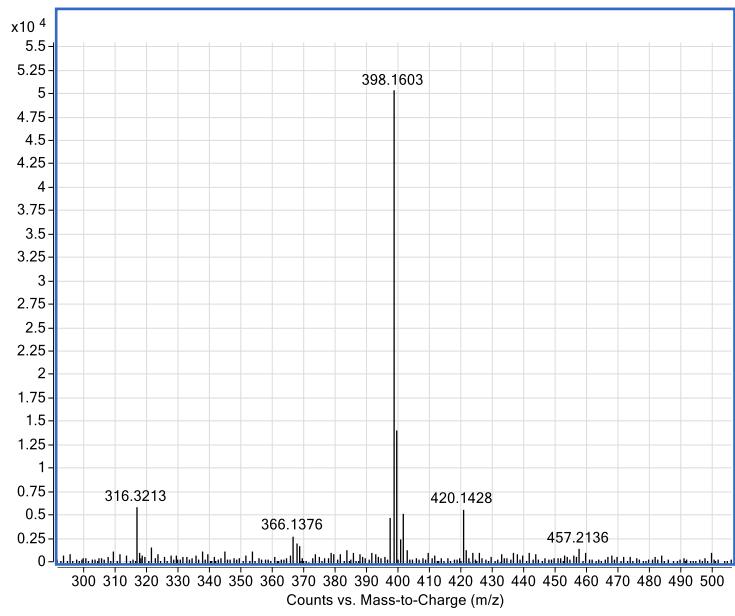


Figure S19. ESI-Q-TOF-MS spectrum of **3**

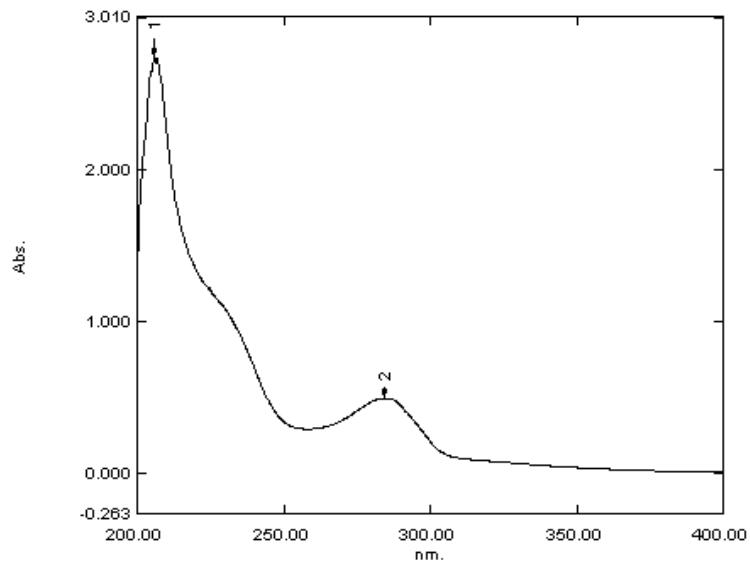


Figure S20. UV spectrum of **3**

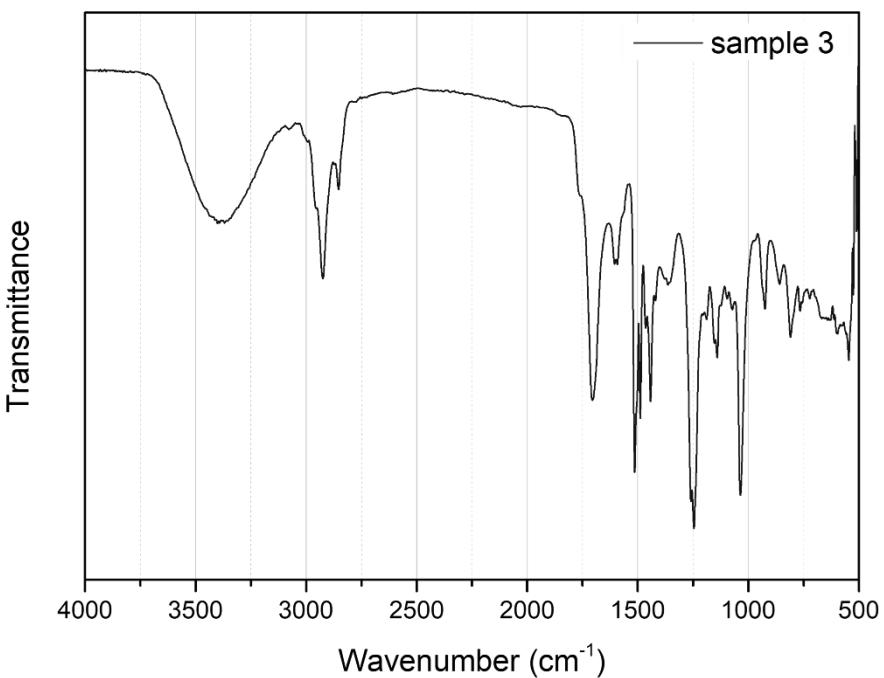


Figure S21. IR spectrum of **3**

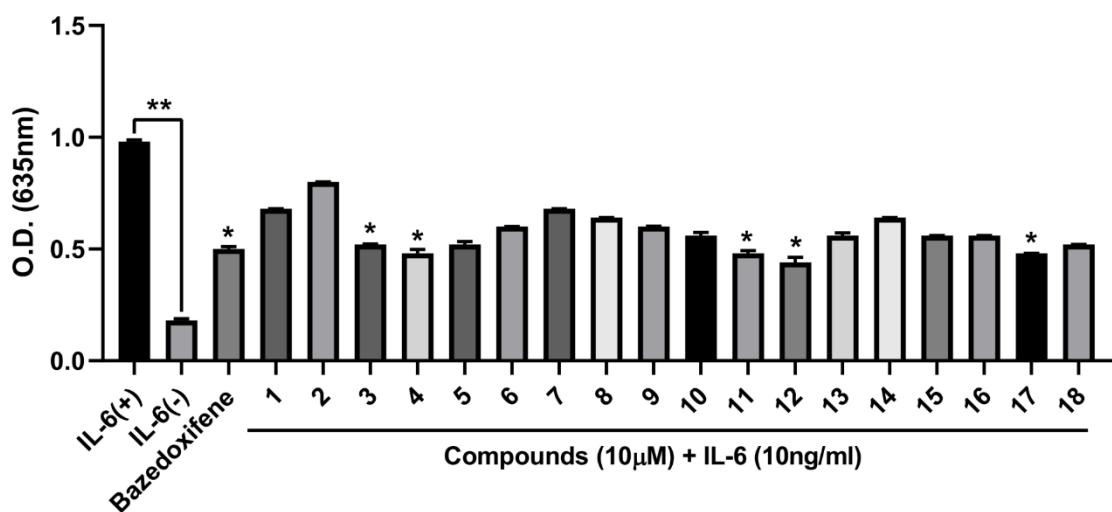


Figure S22. Anti-IL-6 activities of the compounds **1-18** and bazedoxifene (control). Each compound was pre-mixed with 10 ng/ml hIL-6 before the treatment for 24 h. The hIL-6 activities were detected at 635 nm using the QUANTI-blue assay. Data indicate mean \pm SD ($n = 3$). * $p < 0.05$ and ** $p < 0.01$ vs. IL-6 (+)

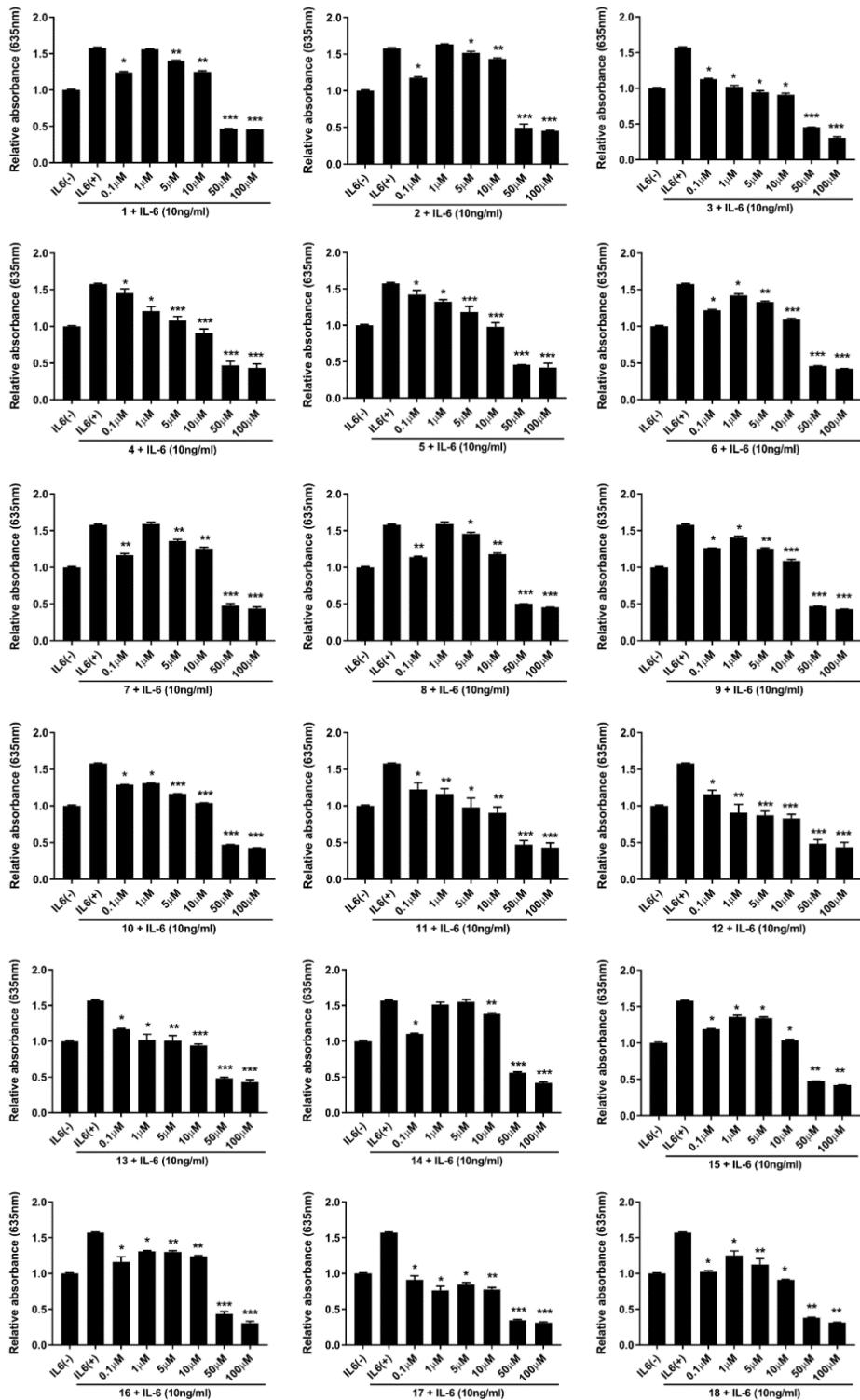


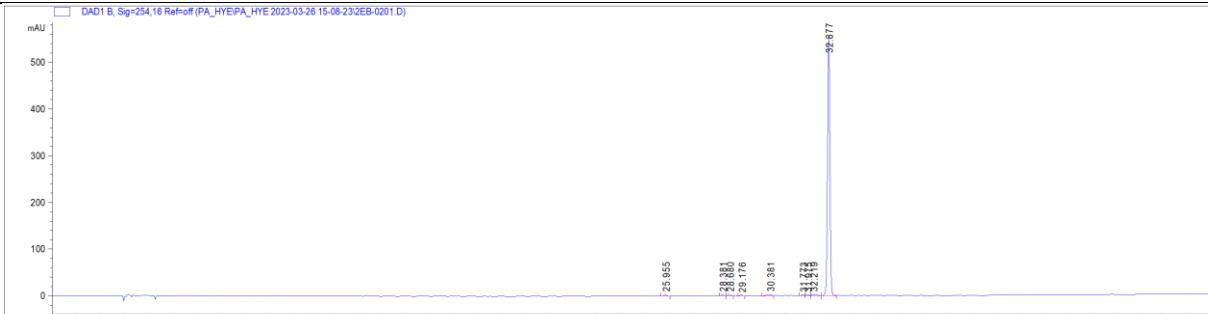
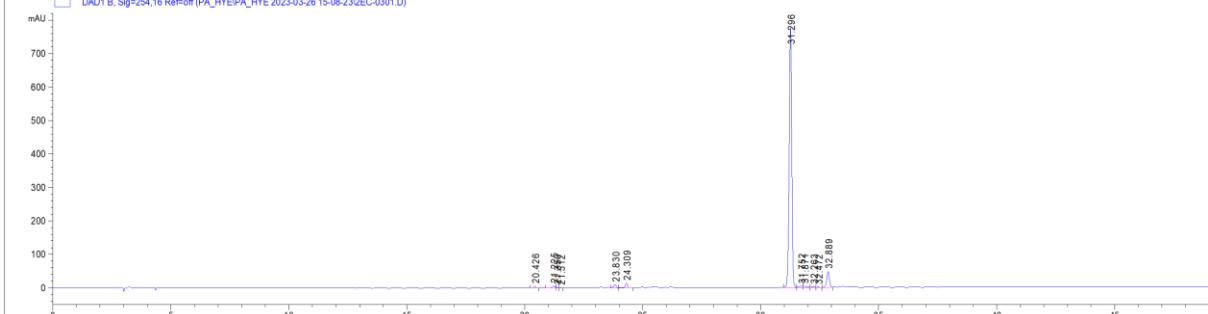
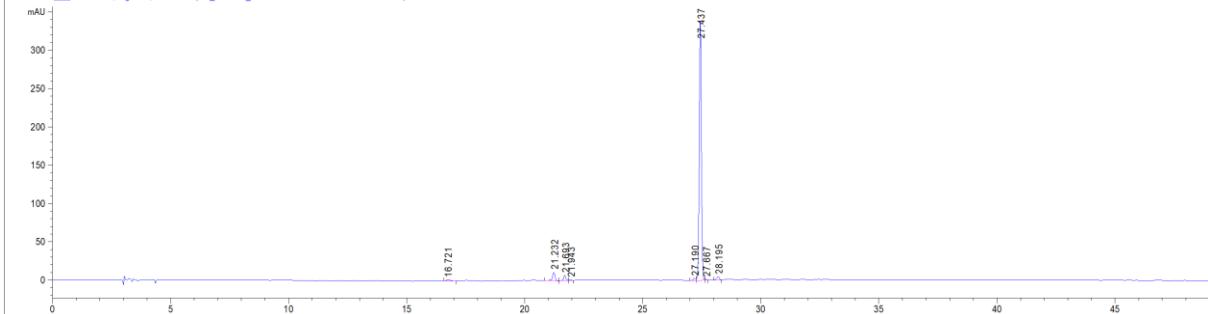
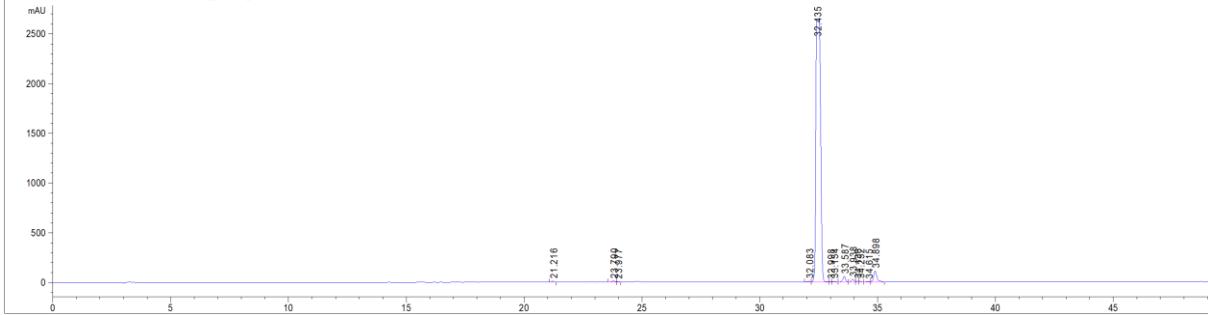
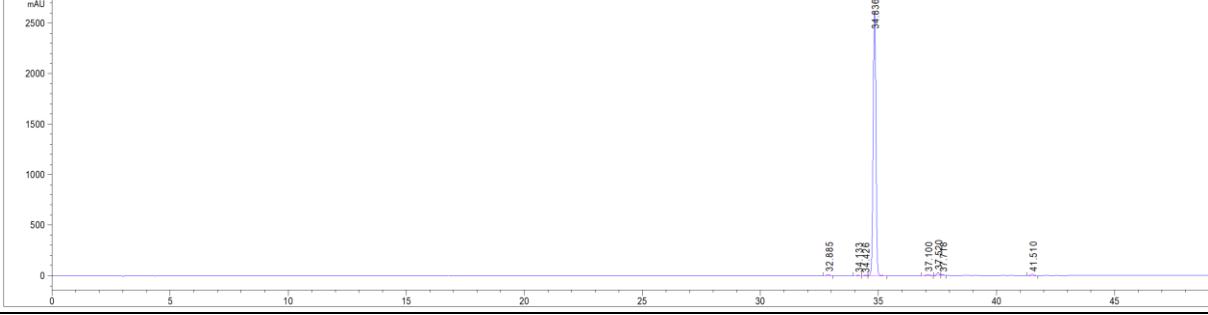
Figure S23. Bioactivity test with eighteen compounds in HEK-Blue™ IL-6 cells. HEK-Blue™ IL-6 cells were treated with various concentration of compounds 1-18 for 24 h. The activation of IL-6 was measured by a SEAP activity assay after the treatment of HEK-Blue™ IL-6 cells with the different indicated concentrations of compounds 1-18 for 30 min in the presence or absence of IL-6 for 24 h. Data indicate mean \pm SD ($n = 3$). * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ vs. IL-6(+).

Table S1. HPLC chromatogram of compounds 1 – 18

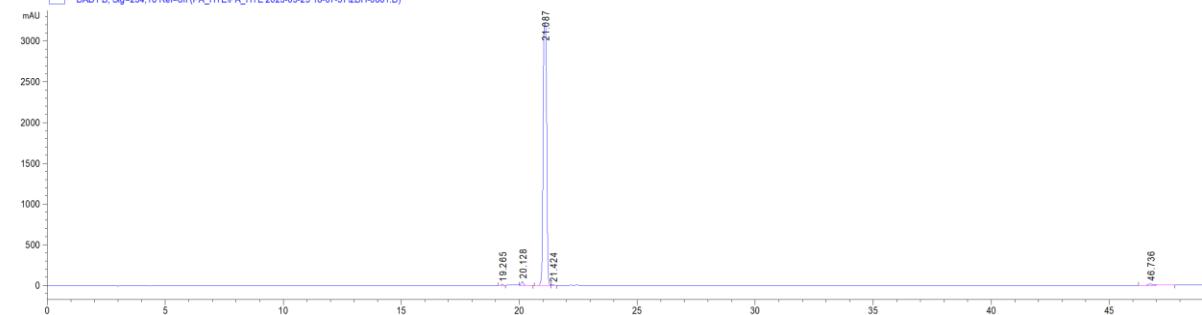
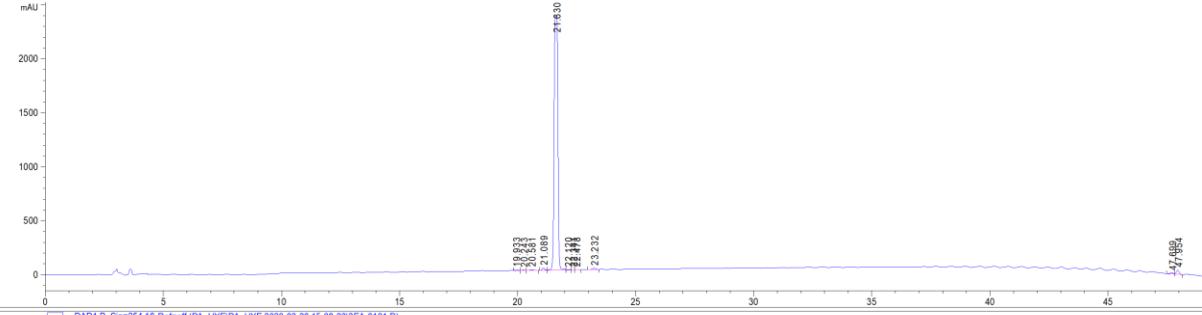
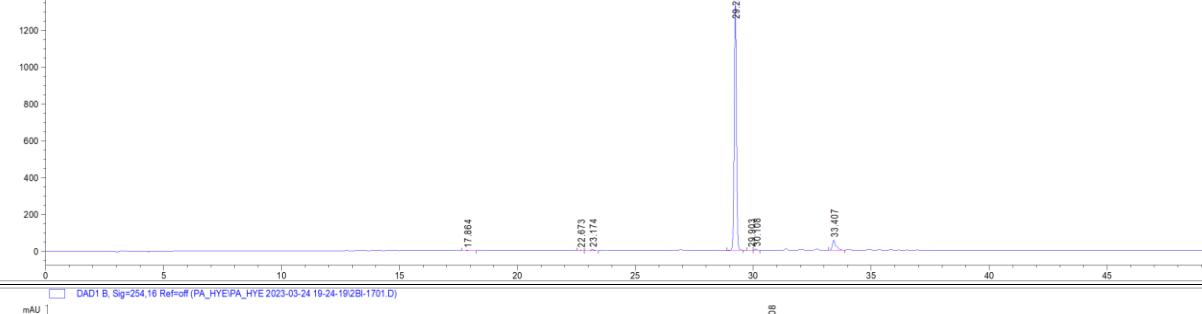
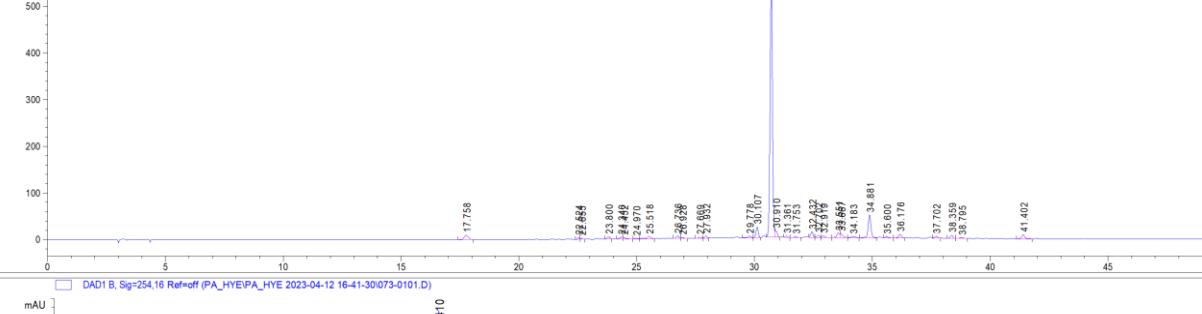
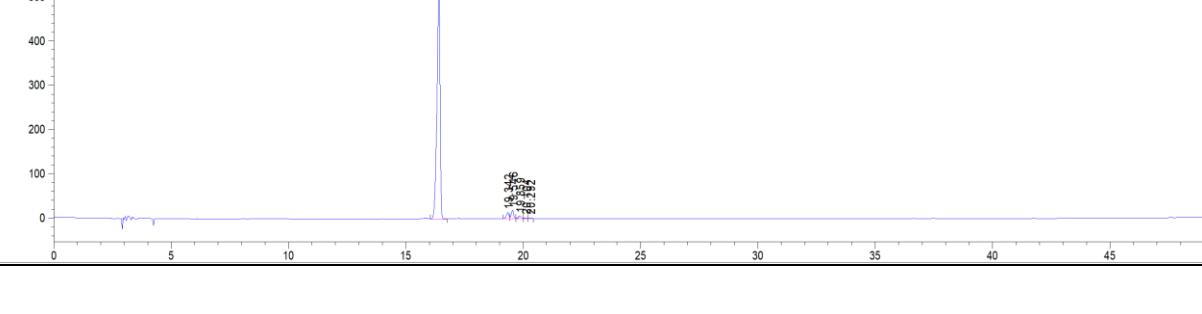
Table S1. Analytical HPLC condition for compounds **1–18**.

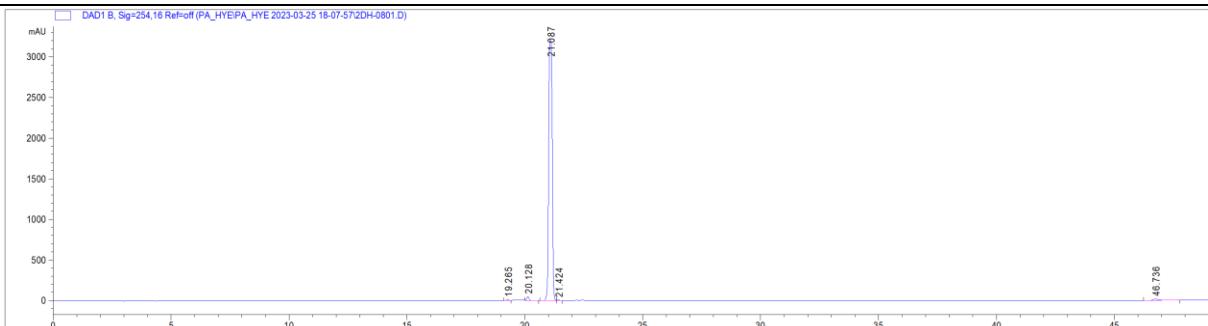
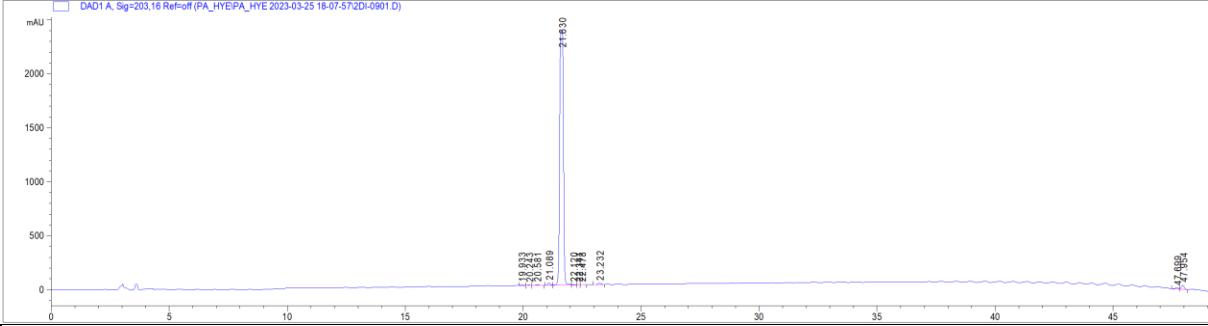
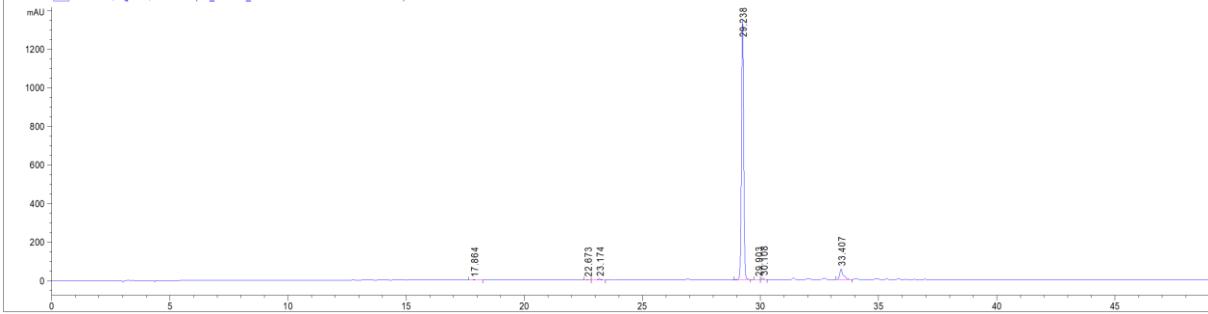
Instrument	Agilent Technologies 1260 Infinity												
HPLC column	Luna C18(2) column (250 × 4.6 mm, 5 µm; Phenomenex)												
Detection wavelength	254 nm for compounds 1–11 and 13–18 203 nm for compound 12												
Flow rate	1.0 mL/min												
Injection volume	20 µL												
Mobile phase condition	<table border="1"> <thead> <tr> <th>Time (min)</th> <th>Water (0.01 % TFA)</th> <th>MeCN (0.01 % TFA)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>95 %</td> <td>5 %</td> </tr> <tr> <td>5</td> <td>95 %</td> <td>5 %</td> </tr> <tr> <td>50</td> <td>0</td> <td>100 %</td> </tr> </tbody> </table>	Time (min)	Water (0.01 % TFA)	MeCN (0.01 % TFA)	0	95 %	5 %	5	95 %	5 %	50	0	100 %
Time (min)	Water (0.01 % TFA)	MeCN (0.01 % TFA)											
0	95 %	5 %											
5	95 %	5 %											
50	0	100 %											

Table S2. HPLC chromatogram for compounds 1–18.

#	HPLC chromatogram	Relative Peak Area (%)
1	 DAD1 B, Sig=254.16 Ref-off (PA_HYE/PA_HYE 2023-03-26 15-08-23\2EB-0201.D) mAU 500 400 300 200 100 0 0 5 10 15 20 25 30 35 40 45 20.426 21.342 25.055 26.880 29.176 30.381 31.233 32.877	95.3
2	 DAD1 B, Sig=254.16 Ref-off (PA_HYE/PA_HYE 2023-03-26 15-08-23\2EC-0301.D) mAU 700 600 500 400 300 200 100 0 0 5 10 15 20 25 30 35 40 45 20.426 21.342 23.930 24.319 31.296 31.692 32.429 33.889	88.9
3	 DAD1 B, Sig=254.16 Ref-off (PA_HYE/PA_HYE 2023-03-26 15-08-23\2ED-0401.D) mAU 300 250 200 150 100 50 0 0 5 10 15 20 25 30 35 40 45 16.721 21.232 21.483 27.190 27.437 27.815	90.8
4	 DAD1 B, Sig=254.16 Ref-off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2DA-0101.D) mAU 2500 2000 1500 1000 500 0 0 5 10 15 20 25 30 35 40 45 21.216 23.797 32.083 32.435 33.988 34.557 35.298 35.508 35.728 35.988	93.6
5	 DAD1 B, Sig=254.16 Ref-off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2DB-0201.D) mAU 2500 2000 1500 1000 500 0 0 5 10 15 20 25 30 35 40 45 32.885 34.423 34.636 35.100 35.728 41.510	97.1

#	HPLC chromatogram	Relative Peak Area (%)
6	<p>DAD1 B, Sig=254,16 Ref-off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2DC-0301.D)</p> <p>mAU</p> <p>400 350 300 250 200 150 100 50 0</p> <p>Y</p> <p>0 5 10 15 20 25 30 35 40 45</p> <p>32.216 37.616 37.635 37.646 37.652 37.658 37.662 37.666 37.671 37.676 37.681 37.686 37.691 37.695 37.699 37.703 37.707 37.711 37.715 37.719 37.723 37.727 37.731 37.735 37.739 37.743 37.747 37.751 37.755 37.759 37.763 37.767 37.771 37.775 37.779 37.783 37.787 37.791 37.795 37.799 37.803 37.807 37.811 37.815 37.819 37.823 37.827 37.831 37.835 37.839 37.843 37.847 37.851 37.855 37.859 37.863 37.867 37.871 37.875 37.879 37.883 37.887 37.891 37.895 37.899 37.903 37.907 37.911 37.915 37.919 37.923 37.927 37.931 37.935 37.939 37.943 37.947 37.951 37.955 37.959 37.963 37.967 37.971 37.975 37.979 37.983 37.987 37.991 37.995 37.999 38.003 38.007 38.011 38.015 38.019 38.023 38.027 38.031 38.035 38.039 38.043 38.047 38.051 38.055 38.059 38.063 38.067 38.071 38.075 38.079 38.083 38.087 38.091 38.095 38.099 38.103 38.107 38.111 38.115 38.119 38.123 38.127 38.131 38.135 38.139 38.143 38.147 38.151 38.155 38.159 38.163 38.167 38.171 38.175 38.179 38.183 38.187 38.191 38.195 38.199 38.203 38.207 38.211 38.215 38.219 38.223 38.227 38.231 38.235 38.239 38.243 38.247 38.251 38.255 38.259 38.263 38.267 38.271 38.275 38.279 38.283 38.287 38.291 38.295 38.299 38.303 38.307 38.311 38.315 38.319 38.323 38.327 38.331 38.335 38.339 38.343 38.347 38.351 38.355 38.359 38.363 38.367 38.371 38.375 38.379 38.383 38.387 38.391 38.395 38.399 38.403 38.407 38.411 38.415 38.419 38.423 38.427 38.431 38.435 38.439 38.443 38.447 38.451 38.455 38.459 38.463 38.467 38.471 38.475 38.479 38.483 38.487 38.491 38.495 38.499 38.503 38.507 38.511 38.515 38.519 38.523 38.527 38.531 38.535 38.539 38.543 38.547 38.551 38.555 38.559 38.563 38.567 38.571 38.575 38.579 38.583 38.587 38.591 38.595 38.599 38.603 38.607 38.611 38.615 38.619 38.623 38.627 38.631 38.635 38.639 38.643 38.647 38.651 38.655 38.659 38.663 38.667 38.671 38.675 38.679 38.683 38.687 38.691 38.695 38.699 38.703 38.707 38.711 38.715 38.719 38.723 38.727 38.731 38.735 38.739 38.743 38.747 38.751 38.755 38.759 38.763 38.767 38.771 38.775 38.779 38.783 38.787 38.791 38.795 38.799 38.803 38.807 38.811 38.815 38.819 38.823 38.827 38.831 38.835 38.839 38.843 38.847 38.851 38.855 38.859 38.863 38.867 38.871 38.875 38.879 38.883 38.887 38.891 38.895 38.899 38.903 38.907 38.911 38.915 38.919 38.923 38.927 38.931 38.935 38.939 38.943 38.947 38.951 38.955 38.959 38.963 38.967 38.971 38.975 38.979 38.983 38.987 38.991 38.995 38.999 39.003 39.007 39.011 39.015 39.019 39.023 39.027 39.031 39.035 39.039 39.043 39.047 39.051 39.055 39.059 39.063 39.067 39.071 39.075 39.079 39.083 39.087 39.091 39.095 39.099 39.103 39.107 39.111 39.115 39.119 39.123 39.127 39.131 39.135 39.139 39.143 39.147 39.151 39.155 39.159 39.163 39.167 39.171 39.175 39.179 39.183 39.187 39.191 39.195 39.199 39.203 39.207 39.211 39.215 39.219 39.223 39.227 39.231 39.235 39.239 39.243 39.247 39.251 39.255 39.259 39.263 39.267 39.271 39.275 39.279 39.283 39.287 39.291 39.295 39.299 39.303 39.307 39.311 39.315 39.319 39.323 39.327 39.331 39.335 39.339 39.343 39.347 39.351 39.355 39.359 39.363 39.367 39.371 39.375 39.379 39.383 39.387 39.391 39.395 39.399 39.403 39.407 39.411 39.415 39.419 39.423 39.427 39.431 39.435 39.439 39.443 39.447 39.451 39.455 39.459 39.463 39.467 39.471 39.475 39.479 39.483 39.487 39.491 39.495 39.499 39.503 39.507 39.511 39.515 39.519 39.523 39.527 39.531 39.535 39.539 39.543 39.547 39.551 39.555 39.559 39.563 39.567 39.571 39.575 39.579 39.583 39.587 39.591 39.595 39.599 39.603 39.607 39.611 39.615 39.619 39.623 39.627 39.631 39.635 39.639 39.643 39.647 39.651 39.655 39.659 39.663 39.667 39.671 39.675 39.679 39.683 39.687 39.691 39.695 39.699 39.703 39.707 39.711 39.715 39.719 39.723 39.727 39.731 39.735 39.739 39.743 39.747 39.751 39.755 39.759 39.763 39.767 39.771 39.775 39.779 39.783 39.787 39.791 39.795 39.799 39.803 39.807 39.811 39.815 39.819 39.823 39.827 39.831 39.835 39.839 39.843 39.847 39.851 39.855 39.859 39.863 39.867 39.871 39.875 39.879 39.883 39.887 39.891 39.895 39.899 39.903 39.907 39.911 39.915 39.919 39.923 39.927 39.931 39.935 39.939 39.943 39.947 39.951 39.955 39.959 39.963 39.967 39.971 39.975 39.979 39.983 39.987 39.991 39.995 39.999 40.003 40.007 40.011 40.015 40.019 40.023 40.027 40.031 40.035 40.039 40.043 40.047 40.051 40.055 40.059 40.063 40.067 40.071 40.075 40.079 40.083 40.087 40.091 40.095 40.099 40.103 40.107 40.111 40.115 40.119 40.123 40.127 40.131 40.135 40.139 40.143 40.147 40.151 40.155 40.159 40.163 40.167 40.171 40.175 40.179 40.183 40.187 40.191 40.195 40.199 40.203 40.207 40.211 40.215 40.219 40.223 40.227 40.231 40.235 40.239 40.243 40.247 40.251 40.255 40.259 40.263 40.267 40.271 40.275 40.279 40.283 40.287 40.291 40.295 40.299 40.303 40.307 40.311 40.315 40.319 40.323 40.327 40.331 40.335 40.339 40.343 40.347 40.351 40.355 40.359 40.363 40.367 40.371 40.375 40.379 40.383 40.387 40.391 40.395 40.399 40.403 40.407 40.411 40.415 40.419 40.423 40.427 40.431 40.435 40.439 40.443 40.447 40.451 40.455 40.459 40.463 40.467 40.471 40.475 40.479 40.483 40.487 40.491 40.495 40.499 40.503 40.507 40.511 40.515 40.519 40.523 40.527 40.531 40.535 40.539 40.543 40.547 40.551 40.555 40.559 40.563 40.567 40.571 40.575 40.579 40.583 40.587 40.591 40.595 40.599 40.603 40.607 40.611 40.615 40.619 40.623 40.627 40.631 40.635 40.639 40.643 40.647 40.651 40.655 40.659 40.663 40.667 40.671 40.675 40.679 40.683 40.687 40.691 40.695 40.699 40.703 40.707 40.711 40.715 40.719 40.723 40.727 40.731 40.735 40.739 40.743 40.747 40.751 40.755 40.759 40.763 40.767 40.771 40.775 40.779 40.783 40.787 40.791 40.795 40.799 40.803 40.807 40.811 40.815 40.819 40.823 40.827 40.831 40.835 40.839 40.843 40.847 40.851 40.855 40.859 40.863 40.867 40.871 40.875 40.879 40.883 40.887 40.891 40.895 40.899 40.903 40.907 40.911 40.915 40.919 40.923 40.927 40.931 40.935 40.939 40.943 40.947 40.951 40.955 40.959 40.963 40.967 40.971 40.975 40.979 40.983 40.987 40.991 40.995 40.999 41.003 41.007 41.011 41.015 41.019 41.023 41.027 41.031 41.035 41.039 41.043 41.047 41.051 41.055 41.059 41.063 41.067 41.071 41.075 41.079 41.083 41.087 41.091 41.095 41.099 41.103 41.107 41.111 41.115 41.119 41.123 41.127 41.131 41.135 41.139 41.143 41.147 41.151 41.155 41.159 41.163 41.167 41.171 41.175 41.179 41.183 41.187 41.191 41.195 41.199 41.203 41.207 41.211 41.215 41.219 41.223 41.227 41.231 41.235 41.239 41.243 41.247 41.251 41.255 41.259 41.263 41.267 41.271 41.275 41.279 41.283 41.287 41.291 41.295 41.299 41.303 41.307 41.311 41.315 41.319 41.323 41.327 41.331 41.335 41.339 41.343 41.347 41.351 41.355 41.359 41.363 41.367 41.371 41.375 41.379 41.383 41.387 41.391 41.395 41.399 41.403 41.407 41.411 41.415 41.419 41.423 41.427 41.431 41.435 41.439 41.443 41.447 41.451 41.455 41.459 41.463 41.467 41.471 41.475 41.479 41.483 41.487 41.491 41.495 41.499 41.503 41.507 41.511 41.515 41.519 41.523 41.527 41.531 41.535 41.539 41.543 41.547 41.551 41.555 41.559 41.563 41.567 41.571 41.575 41.579 41.583 41.587 41.591 41.595 41.599 41.603 41.607 41.611 41.615 41.619 41.623 41.627 41.631 41.635 41.639 41.643 41.647 41.651 41.655 41.659 41.663 41.667 41.671 41.675 41.679 41.683 41.687 41.691 41.695 41.699 41.703 41.707 41.711 41.715 41.719 41.723 41.727 41.731 41.735 41.739 41.743 41.747 41.751 41.755 41.759 41.763 41.767 41.771 41.775 41.779 41.783 41.787 41.791 41.795 41.799 41.803 41.807 41.811 41.815 41.819 41.823 41.827 41.831 41.835 41.839 41.843 41.847 41.851 41.855 41.859 41.863 41.867 41.871 41.875 41.879 41.883 41.887 41.891 41.895 41.899 41.903 41.907 41.911 41.915 41.919 41.923 41.927 41.931 41.935 41.939 41.943 41.947 41.951 41.955 41.959 41.963 41.967 41.971 41.975 41.979 41.983 41.987 41.991 41.995 41.999 42.003 42.007 42.011 42.015 42.019 42.023 42.027 42.031 42.035 42.039 42.043 42.047 42.051 42.055 42.059 42.063 42.067 42.071 42.075 42.079 42.083 42.087 42.091 42.095 42.099 42.103 42.107 42.111 42.115 42.119 42.123 42.127 42.131 42.135 42.139 42.143 42.147 42.151 42.155 42.159 42.163 42.167 42.171 42.175 42.179 42.183 42.187 42.191 42.195 42.199 42.203 42.207 42.211 42.215 42.219 42.223 42.227 42.231 42.235 42.239 42.243 42.247 42.251 42.255 42.259 42.263 42.267 42.271 42.275 42.279 42.283 42.287 42.291 42.295 42.299 42.303 42.307 42.311 42.315 42.319 42.323 42.327 42.331 42.335 42.339 42.343 42.347 42.351 42.355 42.359 42.363 42.367 42.371 42.375 42.379 42.383 42.387 42.391 42.395 42.399 42.403 42.407 42.411 42.415 42.419 42.423 42.427 42.431 42.435 42.439 42.443 42.447 42.451 42.455 42.459 42.463 42.467 42.471 42.475 42.479 42.483 42.487 42.491 42.495 42.499 42.503 42.507 42.511 42.515 42.519 42.523 42.527 42.531 42.535 42.539 42.543 42.547 42.551 42.555 42.559 42.563 42.567 42.571 42.575 42.579 42.583 42.587 42.591 42.595 42.599 42.603 42.607 42.611 42.615 42.619 42.623 42.627 42.631 42.635 42.639 42.643 42.647 42.651 42.655 42.659 42.663 42.667 42.671 42.675 42.679 42.683 42.687 42.691 42.695 42.699 42.703 42.707 42.711 42.715 42.719 42.723 42.727 42.731 42.735 42.739 42.743 42.747 42.751 42.755 42.759 42.763 42.767 42.771 42.775 42.779 42.783 42.787 42.791 42.795 42.799 42.803 42.807 42.811 42.815 42.819 42.823 42.827 42.831 42.835 42.839 42.843 42.847 42.851 42.855 42.859 42.863 42.867 42.871 42.875 42.879 42.883 42.887 42.891 42.895 42.899 42.903 42.907 42.911 42.915 42.919 42.923 42.927 42.931 42.935 42.939 42.943 42.947 42.951 42.955 42.959 42.963 42.967 42.971 42.975 42.979 42.983 42.987 42.991 42.995 42.999 43.00</p>	

#	HPLC chromatogram	Relative Peak Area (%)
11	 <p>DAD1 B, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2DH-0801.D)</p> <p>mAU</p> <p>Peaks labeled: 19.245, 20.128, 21.124, 21.087, 21.630, 46.736</p>	97.7
12	 <p>DAD1 A, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2EA-0901.D)</p> <p>mAU</p> <p>Peaks labeled: 19.233, 20.481, 21.089, 21.630, 22.088, 23.232, 47.084</p>	96.2
13	 <p>DAD1 B, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-03-26 15-08-23\2EA-0101.D)</p> <p>mAU</p> <p>Peaks labeled: 17.884, 21.673, 22.174, 29.238, 29.708, 33.407</p>	92.6
14	 <p>DAD1 B, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-03-24 19-24-19\2B-1701.D)</p> <p>mAU</p> <p>Peaks labeled: 17.758, 22.684, 23.800, 24.369, 25.670, 25.516, 26.736, 27.059, 29.218, 30.070, 30.708, 31.351, 31.753, 32.432, 32.916, 33.667, 34.183, 34.481, 35.600, 36.176, 37.702, 38.359, 38.785, 41.402</p>	68.2
15	 <p>DAD1 B, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-04-12 16-41-30\073-0101.D)</p> <p>mAU</p> <p>Peaks labeled: 16.410, 19.124, 20.128, 21.089, 21.630, 46.736</p>	94.5

#	HPLC chromatogram	Relative Peak Area (%)
16	 <p>DAD1 B, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2D1-0801.D)</p> <p>mAU</p> <p>Peaks labeled: 19.465, 20.128, 21.424, 21.687, 46.736</p>	95.1
17	 <p>DAD1 A, Sig=203,16 Ref=off (PA_HYE/PA_HYE 2023-03-25 18-07-57\2D1-0901.D)</p> <p>mAU</p> <p>Peaks labeled: 18.923, 20.581, 21.089, 21.630, 22.449, 33.232, 47.499</p>	90.9
18	 <p>DAD1 B, Sig=254,16 Ref=off (PA_HYE/PA_HYE 2023-03-26 15-08-23\2EA-0101.D)</p> <p>mAU</p> <p>Peaks labeled: 17.864, 22.873, 23.174, 29.238, 38.988, 33.407</p>	85.6