Additional File 2

Anti-inflammatory effects of novel curcumin analogs in experimental acute lung injury

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Spectral data

Synthesis of morpholine enamines 2a and 2b

To a solution of morpholine (0.12 mol) in dry toluene (70 mL) was added cyclopentanone or cyclohexanone (0.1 mol) dropwise, followed by p-toluenesulfonic acid (1.16 mmol) at room temperature. The mixture solution was then refluxed for 5h. The resulting solution was concentrated in vacuo to give morpholine enamines **2a** and **2b** with the yields of 60-85%.

Synthesis of α,β-unsaturated ketones 3a, 3b, 4a and 4b

A solution of morpholine enamines **2a** or **2b** (3.0 equiv) in Ethanol (15 mL) was added 2-trifluorobenzaldehyde or 2-nitrobenzaldehyde (1 equiv) portion wise. After refluxing for 4-5h, the resulting mixture was acidated to a pH of 5-6 by a solution of 5% HCl, diluted with brine and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by chromatography on silica gel to give desired ketones **3a, 3b, 4a and 4b**.

Synthesis of asymmetric MACs a1-a10, a12-a16, a19, b10-b20 and b22-b25.

To a stirring solution of **3a, 3b, 4a, 4b** (0.37 mmol) and various aromatic aldehydes (0.37 mmol) in EtOH (10 mL) was added 20% NaOH dropwise. The reaction mixture was stirred at room temperature for 10h, then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization or chromatography on silica gel to furnish target MACs **a1-a10, a12-a16, a19, b10-b20 and b22-b25**.

(2E,6E)-2-(4-morpholinobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a1)**

Red powder, 36.7% yield, m.p 176.9-179.4 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.921 (1H, s, H-β), 7.791(1H, s, H-β'), 7.710 (1H, d, *J* = 7.8 Hz, H-3), 7.540 (1H, t, *J* = 7.2 Hz, H-5), 7.469 (2H, d, *J* = 8.4 Hz, H-2', H-6'), 7.418 (1H, t, *J* = 7.8 Hz, H-4), 7.314 (1H, d, *J* = 7.2 Hz, H-6), 6.919 (2H, d, *J* = 8.4 Hz, H-3', H-5'), 3.872 (4H, t, *J* =

4.8 Hz, Ar-morpholine-$CH_2C\underline{H}_2OC\underline{H}_2CH_2$-),3.259 (4H, t, *J* = 4.8 Hz, Ar-morpholine-$C\underline{H}_2CH_2OCH_2C\underline{H}_2$-), 2.935 (2H, t, *J* = 5.4 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.613 (2H, t, *J* = 4.8 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-),1.741-1.782 (2H, m, Cyclohexan-one-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 428.4 $(M+H)^+$.

(2E,6E)-2-(4-(4-methylpiperazin-1-yl)benzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a2)**

Red powder, 50.7% yield, m.p 100.1-102.8 ^oC. ^1H-NMR (600 MHz, DMSO) δ (ppm) 7.825 (1H, s, H-β), 7.727 (2H, d, *J* = 3.6 Hz, H-2', H-6'), 7.594 (2H, d, *J* = 16.2 Hz, H-3, H-6), 7.514 (1H, t, *J* = 7.8 Hz, H-5), 7.470 (1H, s, H-β'), 7.455 (1H, t, *J* = 9 Hz, H-4), 6.995 (2H, d, *J* = 9 Hz, H-3', H-5'), 3.269 [4H, t, *J* = 4.8 Hz, Ar-N-methylpiperaine-$C\underline{H}_2CH_2N(CH_3)CH_2C\underline{H}_2$-], 2.892 (2H, t, *J* = 6 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.612 (2H, t, *J* = 6 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 2.434 [4H, t, *J* = 4.8 Hz, Ar-N-methylpiperaine-$CH_2C\underline{H}_2N(CH_3)C\underline{H}_2CH_2$-], 2.217(3H, s, Ar-N-methylpiperaine-CH_3), 1.625-1.795 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 441.6 $(M+H)^+$.

(2E,6E)-2-(4-(3-(dimethylamino)propoxy)benzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a3)**

Yellow oil, 51.6% yield. ^1H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.894 (1H, s, H-β), 7.825 (1H, s, H-β'), 7.647 (2H, d, *J* = 3.6 Hz, H-2', H-6'), 7.572 (1H, d, *J* = 9 Hz, H-3), 7.564 (1H, d, *J* = 9 Hz, H-5), 7.440 (1H, d, *J* = 7.8 Hz, H-6), 7.344 (1H, t, *J* = 5.4 Hz, H-4), 7.034 (2H, d, *J* = 5.4 Hz, H-3', H-5'), 4.053 [2H, t, *J* = 6.6 Hz, Ar-$OC\underline{H}_2CH_2CH_2N(CH_3)_2$], 2.503 (2H, t, *J* = 1.8 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.497 (2H, t, *J* = 1.8 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 2.364 [2H, t, *J* = 3.6 Hz, Ar-$OCH_2CH_2C\underline{H}_2N(CH_3)_2$], 2.155 [6H, s, Ar-$OCH_2CH_2CH_2N(C\underline{H}_3)_2$], 1.825-1.862 [2H, m, Ar-$OCH_2C\underline{H}_2CH_2N(CH_3)_2$], 1.255-1.412 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 444.4 $(M+H)^+$.

(2E,6E)-2-(4-(piperidin-1-yl)benzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohe xanone **(a4)**

Red oil, 31.7% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.705 (1H, d, *J* = 7.8 Hz, H-2'), 7.633 (1H, d, *J* = 7.8 Hz, H-6'), 7.535 (1H, t, *J* = 7.8 Hz, H-5), 7.478 (1H, s, H-β), 7.440 (1H, d, *J* = 9 Hz, H-3), 7.352 (1H, t, *J* = 9 Hz, H-4), 7.351 (1H, s, H-β'), 7.313 (1H, d, *J* = 7.8 Hz, H-6), 6.905 (1H, d, *J* = 9Hz, H-3'), 6.868 (1H, d, *J* = 8.4 Hz, H-5'), 3.285 (4H, t, *J* = 10.2 Hz, Ar-tetrahydropyridine-$C\underline{H}_2CH_2CH_2CH_2C\underline{H}_2$-), 2.754 (2H, t, *J* = 5.4 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$), 2.604 (2H, t, *J* = 4.8 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.738-1.780 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-), 1.678-1.693 (2H, m, Ar-tetrahydropyridine-$CH_2CH_2C\underline{H}_2CH_2CH_2$-), 1.600-1.632 (4H, m, Ar-tetrahydropyridine-$CH_2C\underline{H}_2CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 426.2 $(M+H)^+$.

(2E,6E)-2-(2-bromo-5-fluorobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a5)**

Yellow oil, 54.6% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.962 (1H, s, H-β), 7.850 (1H, s, H-β'), 7.725 (1H, d, *J* = 7.8 Hz, H-3), 7.598 (1H, d, *J* = 5.4 Hz, H-3'), 7.557 (1H, d, *J* = 7.8 Hz, H-5), 7.441 (1H, t, *J* =7.8 Hz, H-4), 7.330 (1H, d, *J* = 7.8 Hz, H-6), 7.041 (1H, d, *J* = 6.6 Hz, H-4'), 6.22-6.941 (1H, m, H-6'), 2.739 (2H, t, *J* = 4.8Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.647 (2H, t, *J* = 5.4 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.739-1.770 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 439.6 $(M)^+$.

(2E,6E)-2-(2-bromo-6-fluorobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a6)**

Yellow powder, 44.7% yield, m.p 99.2-102.5 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.968 (1H, s, H-β), 7.929 (1H, s, H-β'), 7.724 (1H, d, *J* = 7.8 Hz, H-3), 7.542 (1H, d, *J* = 6 Hz, H-5), 7.532 (1H, t, *J* = 8.4 Hz, H-4), 7.507 (2H, d, *J* = 12 Hz, H-6, H-3'), 7.443 (1H, d *J* = 7.8 Hz, H-5'), 7.416 (1H, t, *J* = 5.4 Hz, H-4'), 2.647 (4H, t, *J* = 6 Hz, Cyclohexanone-$C\underline{H}_2CH_2C\underline{H}_2$-), 1.709-1.729 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 439.4 $(M)^+$.

(2E,6E)-2-(4-bromobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a7)**

Yellow powder, 25.6% yield, m.p 129.7-132.3 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.945 (1H, s, H-β), 7.720 (2H, d, *J* = 9.0 Hz , H-2', H-6'), 7.557 (1H , d, *J* = 7.8 Hz, H-3), 7.537 (2H, d, *J* = 6.4 Hz, H-3', H-5'), 7.434 (1H, t, *J* = 7.2 Hz, H-5), 7.331 (1H, s, H-β'), 7.327 (1H, d, *J* = 6.0 Hz, H-6), 7.317 (1H, t, *J* = 4.2 Hz, H-4), 2.874 (2H, t, *J* = 5.4 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.631 (2H, t, *J* = 5.4 Hz, Cyclohexanone -$CH_2CH_2C\underline{H}_2$-), 1.743-1.763 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 423.1 $(M)^+$.

(2E,6E)-2-(2,5-dibromobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone **(a8)**

Yellow oil, 54.6% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 7.959 (1H, s, H-β), 7.741 (1H, s, H-β'), 7.726 (1H, d, *J* = 7.8 Hz, H-3), 7.599 (1H, t, *J* = 7.2 Hz, H-5), 7.500 (1H, d, *J* = 8.4 Hz, H-3'), 7.448 (1H, d, *J* = 7.2 Hz, H-4'), 7.427 (2H, *t*, *J* = 2.4 Hz, H-4, H-6'), 7.332 (1H, d, *J* = 5.4 Hz, H-6), 2.732 (2H, t, *J* = 4.8 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.648 (2H, t, *J* = 5.4 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-),1.741 -1.761 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 501.3 $(M+H)^+$.

(2E,6E)-2-(3,4-dimethoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexano **(a9)**

Yellow powder, 70.6% yield, m.p 131.8-135.5 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.225 (1H, d, *J* = 7.2 Hz, H-3), 7.947 (1H, s, H-β), 7.792 (1H, s, H-β'), 7.640 (1H, t, *J* = 15.0 Hz, H-4), 7.500 (1H, t, *J* = 15.6 Hz, H-5), 7.370 (1H, d, *J* = 7.8 Hz, H-6), 7.123 (1H, d, *J* = 8,4 Hz, H-6'), 7.027 (1H, s, H-2'), 6.915 (1H, d, *J* = 8.4 Hz, H-5'), 3.928 (3H, s, 3'-OCH_3), 3.914 (3H, s, 4'-OCH_3), 2.949 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.605 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.766-1.808 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 380.1 $(M+H)^+$.

(2E,6E)-2-(2,3-dimethoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexano **(a10)**

Orange powder, 63.2% yield, m.p 124.3-129.1 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.127 (1H, d, *J* = 8.4 Hz, H-3), 7.955 (2H, s, H-β, H-β'), 7.640 (1H, t, *J* = 14.4 Hz, H-4), 7.501 (1H, t, *J* = 14.4 Hz, H-5), 7.376 (1H, d, *J* = 7.8 Hz, H-6), 7.065 (1H, t, *J* = 15.0 Hz, H-5'), 6.930 (2H, d, *J* = 8.4 Hz, H-4', H-6'), 3.889 (3H, s, 2'-OCH_3), 3.834 (3H, s, 3'-OCH_3), 2.804 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$C\underline{H}_2CH_2$ CH_2-), 2.604 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.709-1.750 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 380.0 $(M+H)^+$.

(2E,6E)-2-(2-fluoro-4-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone **(a12)**

Yellow oil, 40.7% yield, ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.125 (1H, d, *J* = 8.4 Hz, H-3), 7.947 (1H, s, H-β), 7.850 (1H, s, H-β'), 7.640 (1H, t, *J* = 14.4 Hz, H-4), 7.500 (1H, t, *J* = 15.6 Hz, H-5), 7.368 (1H, d, *J* = 8.4 Hz, H-6), 7.345 (1H, s, H-3'), 6.727 (1H, d, *J* = 10.8 Hz, H-6'), 6.675 (1H, d, *J* = 14.4 Hz, H-5'), 3.836 (3H, s, 4'-OCH_3), 2.815 (2H, t, *J* = 10.8 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.604 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.738-1.780 (2H, m, Cyclohexanone -$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 368.0 $(M+H)^+$.

(2E,6E)-2-(2-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone **(a13)**

Yellow powder, 69.4% yield, m.p 148.8-153.9 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.119 (1H, d, *J* = 8.4 Hz, H-3), 8.030 (1H, s, H-β), 7.943 (1H, s, H-β'), 7.635 (1H, t, *J* = 14.4 Hz, H-4), 7.495 (1H, t, *J* = 15.6 Hz, H-5), 7.368 (1H, d, *J* = 7.8 Hz, H-6), 7.336 (1H, t, *J* = 15.6 Hz, H-5'), 7.317 (1H, d, *J* = 13.8 Hz, H-6'), 6.967 (1H, t, *J* = 14.4 Hz, H-4'), 6.928 (1H, d, *J* = 8.4 Hz, H-3'), 3.875 (3H, s, 2'-OCH_3), 2.847 (2H, t, *J* = 10.8 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.607 (2H, t, *J* = 10.8 Hz, Cyclohexan one-$CH_2CH_2C\underline{H}_2$-), 1.720-1.761 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 350.1 $(M+H)^+$.

(2E,6E)-2-(3-bromo-4-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone

(a14)

Yellow powder, 66.0% yield, m.p: 183.2-187.2 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.130 (1H, d, *J* = 7.8 Hz, H-3), 7.948 (1H, s, H-2'), 7.712 (2H, s, H-β, H-β'), 7.644 (1H, t, *J* = 15.0 Hz, H-4), 7.505 (1H, t, *J* = 15.0 Hz, H-5), 7.419 (1H, d, *J* = 10.2 Hz, H-6), 7.368 (1H, d, *J* = 7.2 Hz, H-6'), 6.940 (1H, d, *J* = 8.4 Hz, H-5'), 3.942 (3H, s, 4'-OCH_3), 2.910 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.604 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.765-1.807 (2H, m, Cyclohexanone-CH_2 $C\underline{H}_2CH_2$-). ESI-MS m/z: 429.8 $(M+H)^+$.

(2E,6E)-2-(5-bromo-2-ethoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone

(a15)

Yellow powder, 67.8% yield, m.p 154.1-158.6 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.127 (1H, d, *J* = 8.4 Hz, H-3), 7.950 (1H, s, H-β), 7.924 (1H, s, H-β'), 7.643 (1H, t, *J* = 15.0 Hz, H-4), 7.504 (1H, t, *J* = 14.4 Hz, H-5), 7.405 (1H, s, H-6'), 7.374 (2H, d, *J* = 7.8 Hz, H-6, H-3'), 6.787 (1H, d, *J* = 8.4 Hz, H-4'), 4.048-4.083 (2H, m, Ar-$OC\underline{H}_2CH_3$), 2.832 (2H, t, *J* = 12.0 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.615 (2H, t, *J* = 12.0 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.740-1.781 (2H, m, Cyclohexanone -$CH_2C\underline{H}_2CH_2$-), 1.453 (3H, t, *J* = 13.8 Hz, Ar-$OCH_2C\underline{H}_3$). ESI-MS m/z: 443.8 $(M+H)^+$.

(2E,6E)-2-(2-fluoro-5-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone

(a16)

Yellow powder, 77.8% yield, m.p 139.3-144.0 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.133 (1H, d, *J* = 7.8 Hz, H-3), 7.957 (1H, s, H-β), 7.792 (1H, s, H-β'), 7.647 (1H, t, *J* =15.0 Hz, H-4), 7.510 (1H, t, *J* = 15.6 Hz, H-5), 7.373 (1H, d, *J* = 7.8 Hz, H-6), 7.032 (1H, t, *J* = 18 Hz, H-3'), 6.840-6.852 (2H, m, H-4', H-6'), 3.803 (3H, s, 5'-OCH_3), 2.800 (2H, t, *J* = 11.4 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.615 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.735-1.777 (2H, m, Cyclohexanone-CH_2 $C\underline{H}_2CH_2$-). ESI-MS m/z: 367.9 $(M+H)^+$.

(2E,6E)-2-(4-ethoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone **(a19)**
Yellow powder, 67.0% yield, m.p 142.3-143.7 ºC. ^{1}H-NMR (600 MHz, DMSO) δ(ppm) 8.158 (1H, d, *J* = 7.2 Hz, H-3), 7.803 (1H, t, *J* = 13.8 Hz, H-4), 7.756 (1H, s, H-β), 7.652 (1H, t, *J* = 13.8 Hz, H-5), 7.637 (1H, s, H-β'), 7.570 (1H, d, *J* = 7.2 Hz, H-6), 7.540 (2H, d, *J* = 9.0 Hz, H-2', H-6'), 7.014 (2H, d, *J* = 9.0 Hz, H-3', H-5'), 4.071-4.106 (2H, m, 4'-$OC\underline{H}_2CH_3$), 2.896 (2H, t, *J* = 10.8 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.619 (2H, t, *J* = 10.8 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.674-1.715 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-), 1.345 (3H, t, *J* = 13.8 Hz, 4'-$OCH_2C\underline{H}_3$). ESI-MS m/z: 364.9 $(M+H)^+$.

(2E,5E)-2-(2,3-dimethoxybenzylidene)-5-(2-nitrobenzylidene)cyclopentanone **(b10)**
Yellow powder, 60.9% yield, m.p 120.8-124.0 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.072 (1H, d, *J* = 8.4 Hz, H-3), 7.961 (1H, s, H-β), 7.821 (1H, s, H-β'), 7.656 (1H, t, *J* = 14.4 Hz, H-4), 7.573 (1H, d, *J* = 7.2 Hz, H-6), 7.515 (1H, t, *J* = 15.0 Hz, H-5), 7.132 (1H, d, *J* = 7.2 Hz, H-6'), 7.098 (1H, t, *J* = 15.6 Hz, H-5'), 6.972 (1H, d, *J* = 7.8 Hz, H-4'), 3.896 (3H, s, 2'-OCH_3), 3.877 (3H, s, 3'-OCH_3), 3.003 (2H, t, *J* = 7.8 Hz, Cyclopentanone-$C\underline{H}_2CH_2$-), 2.890 (2H, t, *J* = 7.8 Hz, Cyclopentanone-$CH_2C\underline{H}_2$-). ESI-MS m/z: 366.1 $(M+H)^+$.

(2E,5E)-2-(3-bromo-4-methoxybenzylidene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b14)**
Yellow powder, 61.9% yield, m.p 95.4-100.8 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.871 (1H, s, H-2'), 7.813 (1H, s, H-β), 7.748 (1H, d, *J* = 7.8 Hz, H-3), 7. 585 (1H, d, *J* = 7.2 Hz, H-6'), 7.579 (1H, t, *J* = 7.2 Hz, H-5), 7.546 (1H, d, *J* = 8.4 Hz, H-6), 7.470 (1H, t, *J* = 7.2 Hz, H-4), 7.050(1H, s, H-β'), 6.799 (1H, d, *J* = 4.8 Hz, H-5'), 2.969 (2H, t, *J* = 4.2 Hz, Cyclopentanone-$C\underline{H}_2CH_2$-), 2.948 (2H, t, *J* = 4.2 Hz, Cyclopentanone-$CH_2C\underline{H}_2$-). ESI-MS m/z: 439.2 $(M)^+$.

(2E,5E)-2-(4-ethoxybenzylidene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b19)**
Yellow oil, 42.4% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.827 (1H, s, H-β),

7.738 (1H, d, *J* = 7.8 Hz, H-3), 7. 650 (1H, d, *J* = 1.8 Hz, H-6), 7.601 (1H, t, *J* = 7.8 Hz, H-5), 7.583 (1H, s, H-β'), 7.550 (2H, d, *J* = 9 Hz, H-2', H-6'), 7.447 (1H, t, *J* = 7.8 Hz, H-4), 6.951 (2H, d, *J* = 9 Hz, H-3', H-5'), 4.072-4.107 (2H, m, 4'-OC$\underline{H}_2$CH_3), 3.043 (2H, t, *J* = 4.2 Hz, Cyclopentanone-C$\underline{H}_2$CH_2-), 2.970 (2H, t, *J* = 4.2 Hz, Cyclopentanone-CH_2C$\underline{H}_2$-), 1.442 (3H, t, *J* = 7.2 Hz, 4'-OCH_2C$\underline{H}_3$). ESI-MS m/z: 373.2 $(M+H)^+$.

(2E,5E)-2-(2-(trifluoromethyl)benzylidene)-5-(2,4,6-trimethylbenzylidene)cyclopentanone **(b20)**

Yellow powder, 65.4% yield, m.p 135.6-138.5 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.849 (1H, t, *J* = 2.4 Hz, H-5), 7.743 (1H, d, *J* = 7.8 Hz, H-3), 7.671 (1H, s, H-β), 7.569 (1H, s, H-β'), 7.572 (1H, d, *J* = 3.6 Hz, H-6), 7.452 (1H, t, *J* = 4.2 Hz, H-4), 6.899 (2H, s, H-3',H-5'), 2.853 (2H, t, *J* = 7.2 Hz, Cyclopentanone-C$\underline{H}_2$CH_2-), 2.470 (2H, t, *J* = 7.2 Hz, Cyclopentanone-CH_2C$\underline{H}_2$-), 2.299 (3H, s, 4'-CH_3), 2.189 (6H, s, 2'-CH_3, 6'-CH_3). ESI-MS m/z: 371.5 $(M+H)^+$.

(2E,5E)-2-(2-bromo-4,5-dimethoxybenzylidene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b22)**

Yellow powder, 45.8% yield, m.p 177.8-179.1 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.853 (2H, s, H-β, H-β'), 7.745 (1H, d, *J* = 7.8 Hz, H-3), 7. 578 (1H, t, *J* = 6.6 Hz, H-5), 7.568 (1H, d, *J* = 6.6 Hz, H-6), 7.460 (1H, t, *J* = 6 Hz, H-4), 7.138 (1H, s, H-3'), 7.075 (1H, s, H-6'), 3.922 (3H, s, 5'-OCH_3), 3.888 (3H, s, 4'-OCH_3), 2.996 (2H, t, *J* = 3.6 Hz, Cyclopentanone-C$\underline{H}_2$CH_2-), 2.961 (2H, t, *J* = 3.6 Hz, Cyclopentanone-CH_2C$\underline{H}_2$-). ESI-MS m/z: 469.0 $(M)^+$.

(2E,5E)-2-((5-methylthiophen-2-yl)methylene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b23)**

Yellow oil, 66.7% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.799 (1H, s, H-β), 7.731 (1H, d, *J* = 7.8 Hz, H-3), 7.604 (1H, s, H-β'), 7.610 (1H, d, *J* = 7.2 Hz, H-3'), 7.585 (1H, t, *J* = 7.2 Hz, H-5), 7.446 (1H, t, *J* = 3.6 Hz, H-4), 7.234 (1H, d, *J* = 3.6 Hz, H-6), 6.841 (1H, d, *J* = 3 Hz, H-4'), 2.989 (2H, t, *J* = 6 Hz, Cyclopentanone-C<u>H</u>$_2$CH$_2$-), 2.927 (2H, t, *J* = 6 Hz, Cyclopentanone-CH$_2$C<u>H</u>$_2$-), 2.563 (3H,s, thiophen-CH$_3$). ESI-MS m/z: 349.2 $(M+H)^+$.

(2E,5E)-2-((3-methylthiophen-2-yl)methylene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b24)**

Yellow powder, 65.4% yield, m.p 139.7-142.7 ^oC. ^{1}H-NMR (600 MHz, CDCl$_3$) δ (ppm) 7.932 (1H, s, H-β), 7.818 (1H, s, H-β'), 7.739 (1H, d, *J* = 8.4 Hz, H-5'), 7.618 (1H, d, *J* = 7.8 Hz, H-3), 7.590 (1H, t, *J* = 7.8 Hz, H-5), 7.488 (1H, d, *J* = 5.4 Hz, H-4'), 7.450 (1H, t, *J* = 7.2 Hz, H-4), 7.005 (1H, d, *J* = 5.4 Hz, H-6) 3.001 (2H, t, *J* = 3.6 Hz, Cyclopentanone-C<u>H</u>$_2$CH$_2$-), 2.969 (2H, t, *J* = 3.6 Hz, Cyclopentanone-CH$_2$C<u>H</u>$_2$-), 2.462 (3H, s, thiophen-CH$_3$). ESI-MS m/z: 349.8 $(M+H)^+$.

(2E,5E)-2-((5-bromo-1H-indol-3-yl)methylene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b25)**

Red powder, 35.4% yield, m.p 113.2-116.8 ^oC. ^{1}H-NMR (600 MHz, DMSO) δ (ppm) 12.189 (1H, s, -NH), 8.077 (1H, s, H-2'), 7.948 (1H, s, H-β), 7.897 (1H, d, *J* = 2.4 Hz, H-3), 7.763 (1H, t, *J* = 7.2 Hz, H-4), 7.701 (1H, d, *J* = 8.4 Hz, H-6), 7.596 (1H, s, H-β'), 7.587 (1H, s, H-4'), 7.575(1H, d, *J* =3.6 Hz, H-6'), 7.547 (1H, d, *J* = 2.4 Hz, H-7'), 7.440 (1H, t, *J* = 8.4 Hz, H-5), 3.047 (2H, t, *J* = 6.6 Hz, Cyclopentanone-C<u>H</u>$_2$CH$_2$-), 2.912 (2H, t, *J* = 6.6 Hz, Cyclopentanone-CH$_2$C<u>H</u>$_2$-). ESI-MS m/z: 446.1 $(M)^+$.

General procedure for synthesis of a11, a17,a18 and b21

To a solution of enamine **2a** or **2b** (0.40 mmol) and corresponding arylaldehyde (0.40 mmol) in EtOH (5 mL) was catalyzed by dry hydrogen chloride at room temperature. After 24 h, the resulting solution was diluted with saturated aqueous $NaHCO_3$, the EtOH was then removed under reduced pressure and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was further purified by flash column chromatography to provide MACs analogs **a11, a17, a18 and b21.**

(2E,6E)-2-(2-hydroxy-3-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone **(a11)**

Yellow powder, 65.7% yield, m.p 151.0-154.1 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.117 (1H, t, *J* = 16.8 Hz, H-4), 8.005 (1H, d, *J* = 7.8 Hz, H-3), 7.700 (1H, s, H-β), 7.669 (1H, s, H-β'), 7.598 (1H, t, *J* = 15.0 Hz, H-5), 7.556 (1H, d, *J* = 7.2 Hz, H-6), 7.482 (1H, t, *J* = 15.6 Hz, H-5'), 6.943 (1H, d, *J* = 7.8 Hz, H-6'), 6.768 (1H, d, *J* = 7.8 Hz, H-4'), 4.495 (1H, s, Ar-OH), 3.898 (3H, s, 3'-OCH_3), 2.671 (2H, t, *J* = 15.8 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.557 (2H, t, *J* = 15.8 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.789-1.837 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 364.9 M^+.

(2E,6E)-2-(4-hydroxy-3-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone **(a17)**

Orange powder, 50.6% yield, m.p 165.4-167.1 ºC. ^{1}H-NMR (600 MHz, DMSO) δ(ppm) 9.608 (1H, s, Ar-OH), 8.154 (1H, d, *J* = 8.4 Hz, H-3), 7.800 (1H, t, *J* = 15.0 Hz, H-4), 7.748 (1H, s, H-β), 7.649 (1H, t, *J* = 15.6 Hz, H-5), 7.7624 (1H, s, H-β'), 7.568 (1H, d, *J* = 7.8 Hz, H-6), 7.153 (1H, s, H-2'), 7.078 (1H, d, *J* = 10.2 Hz, H-5'), 6.868 (1H, d, *J* = 8.4 Hz, H-6'), 3.816 (3H, s, Ar-OCH_3), 2.918 (2H, t, *J* = 10.2 Hz, Cyclohexanone-$C\underline{H}_2CH_2CH_2$-), 2.612 (2H, t, *J* = 10.8 Hz, Cyclohexanone-$CH_2CH_2C\underline{H}_2$-), 1.678-1.719 (2H, m, Cyclohexanone-$CH_2C\underline{H}_2CH_2$-). ESI-MS m/z: 365.9 $(M)^+$.

(2E,6E)-2-(3-hydroxy-4-methoxybenzylidene)-6-(2-nitrobenzylidene)cyclohexanone **(a18)**

Yellow powder, 47.0% yield, m.p 166.4-170.8 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.122 (1H, d, *J* = 8.4 Hz, H-3), 7.940 (1H, s, H-β), 7.750 (1H, s, H-β'), 7.638 (1H, t, *J* = 15.0 Hz, H-4), 7.490 (1H, t, *J* = 17.4 Hz, H-5), 7.367 (1H, d, *J* = 7.8 Hz, H-6), 7.123 (1H, s, H-2'), 7.033 (1H, d, *J* = 15.0 Hz, H-6'), 6.888 (1H, d, *J* = 8.4 Hz, H-5'), 5.534 (1H, s, 3'-OH), 3.939 (3H, s, 4'-OCH_3), 2.932 (2H, t, *J* = 10.8 Hz, Cyclohexanone-C<u>H</u>$_2$$CH_2$$CH_2$-), 2.595 (2H, t, *J* = 10.8 Hz, Cyclohexanone-$CH_2$$CH_2$C<u>H</u>$_2$-), 1.750-1.791 (2H, m, Cyclohexanone-CH_2C<u>H</u>$_2$$CH_2$-). ESI-MS m/z: 364.9 ($M^+$).

(2E,5E)-2-(3-bromo-4-hydroxybenzylidene)-5-(2-(trifluoromethyl)benzylidene)cyclopentanone **(b21)**

Yellow powder, 53.2% yield, m.p 164.2-166.9 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 7.845 (1H, s, H-2'), 7.747 (1H, d, *J* = 7.8 Hz, H-3), 7.666 (1H, d, *J* = 7.8 Hz, H-6'), 7.601 (1H, s, H-β), 7. 598 (1H, d, *J* = 4.2 Hz, H-6), 7.504 (1H, s, H-β'), 7.474 (1H, t, *J* = 6 Hz, H-5), 7.421 (1H, t, *J* = 6 Hz, H-4), 7.086 (1H, d, *J* = 8.4 Hz, H-5'), 3.033 (2H, t, *J* = 6 Hz, Cyclopentanone-C<u>H</u>$_2$$CH_2$-), 2.979 (2H, t, *J* = 6 Hz, Cyclopentanone-CH_2C<u>H</u>$_2$-). ESI-MS m/z: 422.9 $(M)^+$.

Synthesis of α,β-unsaturated ketones 5a, 5b

To a solution of 3,4-dimethoxybenzaldehyde or 2-methoxybenzaldehyde (1.00 equiv) in acetone (15 mL) was added 20% NaOH dropwise (1 mL). After stirring at room temperature for 4 h, the resulting mixture was diluted with brine and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by chromatography on silica gel to give desired ketones **5a, 5b**.

General procedure for synthesis of c9, c26

To a solution of 3,4-dimethoxybenzaldehyde or 2-methoxybenzaldehyde (1.0 equiv) and 2-nitrobenzaldehyde (1.0 equiv) in dioxane suspension (15 mL), which NaOH power was added in dioxane, was added 20% NaOH dropwise (0.5 mL). After stirring at room temperature for 5 h, the resulting mixture was diluted with brine and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by chromatography on silica gel to afford target compounds **c9, c26**.

(1E,4E)-1-(3,4-dimethoxyphenyl)-5-(2-nitrophenyl)penta-1,4-dien-3-one **(c9)**

Yellow powder, 70.0% yield, m.p 115.4-120.1 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.106 (1H, d, *J* = 16.2 Hz, H-β), 8.073 (1H, d, *J* = 8.4 Hz, H-3), 7.733 (1H, d, *J* = 16.2 Hz, H-β'), 7.725 (1H, d, *J* = 6.6 Hz, H-6), 7.678 (1H, t, *J* = 15.0 Hz, H-4), 7.562 (1H, t, *J* = 15.0 Hz, H-5), 7.225 (1H, d, *J* = 10.2 Hz, H-6'), 7.147 (1H, s, H-2'), 6.978 (1H, d, *J* = 16.2 Hz, H-α), 6.930 (1H, d, *J* = 15.6 Hz, H-α'), 6.906 (1H, d, *J* = 6.6 Hz, H-5'), 3.950 (3H, s, 3'-OCH_3), 3.938 (3H, s, 4'-OCH_3). ESI-MS m/z: 340.1 $(M+H)^+$.

(1E,4E)-1-(2-methoxyphenyl)-5-(2-nitrophenyl)penta-1,4-dien-3-one **(c26)**

Yellow powder, 60.1% yield, m.p 141.9-144.3 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ(ppm) 8.122 (1H, d, *J* = 16.2 Hz, H-β), 8.079 (1H, d, *J* = 15.6 Hz, H-β'), 8.068 (1H, d, *J* = 6.6 Hz, H-3), 7.738 (1H, d, *J* = 7.2 Hz, H-6), 7.678 (1H, t, *J* = 15.0 Hz, H-4), 7.611 (1H, d, *J* = 6.0 Hz, H, H-6'), 7.555 (1H, t, *J* = 15.6 Hz, H-5), 7.390 (1H, t, *J* = 16.2 Hz, H-4'), 7.228 (1H, d, *J* = 16.2 Hz, H-α), 7.000 (1H, t, *J* = 10.8 Hz, H-5'), 6.961 (1H, d, *J* = 15.6 Hz, H-α'), 6.949 (1H, d, *J* = 8.4 Hz, H-3'), 3.933 (3H, s, 2'-OCH_3). ESI-MS m/z: 310.3 $(M+H)^+$.