**Supporting Information**

**The cytoprotective effects of *E*--(4-methoxyphenyl)-2’,3,4,4'-tetra­methoxychalcone (*E*--*p*-OMe-C6H4-TMC) - A novel and non-cytotoxic HO-1 inducer**

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General experimental information

All reactions were carried out under N2 atmosphere in oven-heated glassware (110 °C) when dry conditions were required, and monitored by TLC on silica gel plates 60 F254 by Merck (Germany). Spots were detected under UV light ( = 254 and 366 nm) or visualized by staining with vanillin/H2SO4 (6.0 g vanillin in 100 mL 95% EtOH/conc. H2SO4 100:1). Column chromatography was performed on silica gel Geduran Si 60 (0.063-0.200 mm) by Merck. Preparative plates were prepared using silica gel 60 GF254 by Merck. Melting points are determined with an automated melting point system (OptiMelt apparatus, USA) and were uncorrected. IR spectroscopy was carried on a Specac Golden Gate Diamond Single Reflection ATR System Excalibur Series FTS3000MX by Bio-Rad (Germany). NMR spectra were recorded on Bruker spectrometer (USA): Avance 300. 1H NMR spectra are referenced to CDCl3 (7.26 ppm); 13C NMR spectra to CDCl3 (77.0 ppm). The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet. Mass spectra were obtained on Agilent Technologies 6540 UHD (USA). The samples for X-ray analysis were recrystallized from EtOAc/hexanes and DCM/hexanes by vapor diffusion technique. All reagents were purchased from commercial sources and were used without further purification. Solvents were distilled before use and dried if water-free conditions were necessary

Analytical data of *Z*--(4-methoxyphenyl)-2’,3,4,4'-tetramethoxychalcone

***Z*--(4-Methoxyphenyl)-2’,3,4,4'-tetramethoxychalcone (*Z*--*p*-OMe-C6H4-TMC)**

Yellow solid, mp 102-103 ºC; 1H NMR (400 MHz, CDCl3): δ = 7.91 (d, *J* = 8.8 Hz, 1H), 7.36 (m, 2H), 6.85 (m, 5H), 6.70 (d, 1H, *J* = 8.8 Hz), 6.42 (dd, 1H, *J* = 8.8, 2.3 Hz), 6.35 (d, 1H, *J* = 2.3 Hz), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H) ppm; 13C NMR (101 MHz, CDCl3): δ = 196.5, 165.1, 161.8, 159.2, 148.4, 148.3, 142.3, 134.6, 131.1, 129.4, 127.6 (2C), 126.1, 121.8, 120.3, 113.9 (2C), 111.4, 110.8, 105.2, 98.6, 55.7, 55.6, 55.4 (2C), 55.2 ppm; IR (neat): 3001, 2937, 2839, 1640, 1592, 1510, 1481, 1245, 1208, 1178, 1021, 958, 891, 828, 768 cm-1; MS (ESI) *m*/*z* (%): 435.18 [MH+](100), 257.58 (1); HRMS (ESI): calcd. for C26H26O6 [MH+] 435.1808; found 435.1802.

X-Ray data of (*E*)--(4-methoxyphenyl)-2’,3,4,4'-tetramethoxychalcone and (*Z*)--(4-methoxyphenyl)-2’,3,4,4'-tetramethoxychalcone

**(*E*)--(4-methoxyphenyl)-2’,3,4,4'-tetramethoxychalcone (*E*--*p*-OMe-C6H4-TMC)**

CCDC no.: 1413001

The dihedral angle between the two aromatic rings (A-ring and B-Ring) is: 69.61°.

*Crystal data and structure refinement*

|  |  |
| --- | --- |
| Empirical formula | C26H26O6 |
| Formula weight | 434.47 |
| Temperature/K | 123.02(10) |
| Crystal system | monoclinic |
| Space group | Pn |
| a/Å | 13.1353(5) |
| b/Å | 13.0590(4) |
| c/Å | 25.9867(9) |
| α/° | 90 |
| β/° | 94.908(4) |
| γ/° | 90 |
| Volume/Å3 | 4441.3(3) |
| Z | 8 |
| ρcalcg/cm3 | 1.300 |
| μ/mm‑1 | 0.753 |
| F(000) | 1840.0 |
| Crystal size/mm3 | 0.16 × 0.14 × 0.05 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection/° | 7.304 to 127.98 |
| Index ranges | -15 ≤ h ≤ 14, -15 ≤ k ≤ 15, -29 ≤ l ≤ 29 |
| Reflections collected | 8480 |
| Independent reflections | 8480 [Rint = N/A, Rsigma = 0.0228] |
| Data/restraints/parameters | 8480/2/1174 |
| Goodness-of-fit on F2 | 1.044 |
| Final R indexes [I>=2σ (I)] | R1 = 0.0555, wR2 = 0.1539 |
| Final R indexes [all data] | R1 = 0.0625, wR2 = 0.1596 |
| Largest diff. peak/hole / e Å-3 | 0.31/-0.26 |
| Flack parameter | -0.4(3) |

***Z*--(4-methoxyphenyl)-2’,3,4,4'-tetramethoxychalcone (*Z*--*p*-OMe-C6H4-TMC)**

CCDC no.: 1413000

*Crystal data and structure refinement*

|  |  |
| --- | --- |
| Empirical formula | C26H26O6 |
| Formula weight | 434.47 |
| Temperature/K | 123.01(10) |
| Crystal system | triclinic |
| Space group | P-1 |
| a/Å | 12.2050(6) |
| b/Å | 13.9442(5) |
| c/Å | 14.1638(6) |
| α/° | 77.245(3) |
| β/° | 69.721(4) |
| γ/° | 88.906(3) |
| Volume/Å3 | 2200.96(17) |
| Z | 4 |
| ρcalcg/cm3 | 1.311 |
| μ/mm‑1 | 0.759 |
| F(000) | 920.0 |
| Crystal size/mm3 | 0.208 × 0.116 × 0.07 |
| Radiation | CuKα (λ = 1.54184) |
| 2Θ range for data collection/° | 6.834 to 147.202 |
| Index ranges | -15 ≤ h ≤ 13, -17 ≤ k ≤ 17, -17 ≤ l ≤ 17 |
| Reflections collected | 30509 |
| Independent reflections | 8689 [Rint = 0.0334, Rsigma = 0.0261] |
| Data/restraints/parameters | 8689/0/587 |
| Goodness-of-fit on F2 | 1.031 |
| Final R indexes [I>=2σ (I)] | R1 = 0.0415, wR2 = 0.1064 |
| Final R indexes [all data] | R1 = 0.0509, wR2 = 0.1137 |
| Largest diff. peak/hole / e Å-3 | 0.26/-0.24 |

Supporting Table S1: Parameters of kinetic measurements

**Table S1** Wavelengths, fold thiol and time intervals (Δt) used in the kinetic assay.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound | Wavelength / nm | [Compound]  / µM | Fold thiol*a* | Δt / s |
| ***Z*--*p*-OMe-C6H4-TMC** | 315 | 40 | 1000-5000 | 1020 |

Fold thiol: **1000-5000:** 1000, 2000, 3000, 4000, 5000. *a* Cysteamine

1H NMR spectrum of *Z*--*p*-OMe-C6H4-TMC in CDCl3 at 400 MHz





13C NMR spectrum of *Z*--*p*-OMe-C6H4-TMC in CDCl3 at 101 MHz



