

## SUPPLEMENTARY MATERIALS

- 1) Main  $^1\text{H}$  NMR and MS characteristics of compounds **1**, **3**, **4**, **6**, **9**, **11-13**, **15**, **17**, **5**, **14**, **7**, **8**, **19**, **18**, and **20-24** (in the order of appearance in paragraphs a) to h) in Materials and Methods) as well as those of some of their precursors.

*4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-1-(4-terbutylphenyl)butan-1-one*, **1**: 69 % yield.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.32 (9H, s), 1.44 (4H, m), 1.97 (4H, m), 2.41 (3H, m), 2.94 (4H, m), 7.17 (2H, t,  $J = 7.1$  Hz), 7.28 (6H, m), 7.45 (4H, d,  $J = 7.1$  Hz), 7.88 (2H, d,  $J = 8.2$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ): m/z 470 ( $\text{M} + \text{H}^+$ ), 452, 268, 250, 203, 161

*4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-1-(4-ethylphenyl)butan-1-one*, **3**: 26 % yield.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.3 (3H, t,  $J = 7.6$  Hz), 1.46 (4H, m), 1.99 (4H, m), 2.43 (3H, m), 2.68 (2H, q,  $J = 7.6$  Hz), 2.97 (4H, m), 7.15 (2H, t,  $J = 7.3$  Hz), 7.27 (6H, m), 7.44 (4H, d,  $J = 7.3$  Hz), 7.87 (2H, d,  $J = 8.0$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ): m/z 442 ( $\text{M} + \text{H}^+$ ), 424, 268, 250, 175, 133.

*4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-1-(4-propylphenyl)butan-1-one*, **4**: 69 % yield.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.92 (3H, t,  $J = 7.6$  Hz), 1.43 (4H, m), 1.64 (2H, t,  $J = 7.6$  Hz), 1.92 (4H, m), 2.37 (3H, m), 2.62 (2H, t,  $J = 7.6$  Hz), 2.93 (4H, m), 7.15 (2H, t,  $J = 7.3$  Hz), 7.25 (6H, m), 7.45 (4H, d,  $J = 7.3$  Hz), 7.86 (2H, d,  $J = 8.2$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ): m/z 456 ( $\text{M} + \text{H}^+$ ), 438, 268, 250, 189, 147.

*1-(4-Butylphenyl)-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butan-1-one*, **6**: 70 % yield.  $^1\text{H}$

NMR ( $\text{CDCl}_3$ ):  $\delta$  0.91 (3H, t,  $J = 7.6$  Hz), 1.33 (2H, m), 1.51-1.61 (6H, m), 1.98 (2H, m), 2.16 (2H, m), 2.51 (3H, m), 2.64 (2H, t,  $J = 7.6$  Hz), 3.01 (4H, m), 7.15 (2H, t,  $J = 7.3$  Hz), 7.25 (6H, m), 7.45 (4H, d,  $J = 7.3$  Hz), 7.85 (2H, d,  $J = 8.2$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ): m/z 470 ( $\text{M} + \text{H}^+$ ), 452, 250, 203, 161.

*2-(4-{4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-1-oxobutyl}phenyl)ethyl acetate* (precursor of compound **7**): 47 % yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.49 (4H, m), 1.95 (4H, m), 2.00 (3H, s), 2.46 (3H, m), 2.97 (6H, m), 4.29 (2H, t,  $J = 6.8 \text{ Hz}$ ), 7.16 (2H, t,  $J = 7.4 \text{ Hz}$ ), 7.27 (6H, m), 7.45 (4H, d,  $J = 7.4 \text{ Hz}$ ), 7.88 (2H, d,  $J = 8.0 \text{ Hz}$ ).

*3-(4-{4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-1-oxobutyl}phenyl)propyl acetate*, **9**: 54 % yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.58 (4H, m), 1.96 (4H, m), 2.03 (3H, m), 2.15 (2H, m), 2.45 (1H, m), 2.53 (2H, m), 2.73 (2H, t,  $J = 7.0 \text{ Hz}$ ), 2.99 (2H, t,  $J = 6.7 \text{ Hz}$ ), 3.08 (2H, m), 4.06 (2H, t,  $J = 7.0 \text{ Hz}$ ), 7.16 (2H, t,  $J = 7.4 \text{ Hz}$ ), 7.27 (6H, m), 7.45 (4H, d,  $J = 7.4 \text{ Hz}$ ), 7.87 (2H, d,  $J = 7.8 \text{ Hz}$ ).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  514 ( $\text{M} + \text{H}^+$ ), 454, 250, 247, 205, 187.

*1-(4-Bromophenyl)-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butan-1-one*, **11**: 40 % yield. mp = 102-110°C.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.50 (4H, m), 1.97 (4H, m), 2.45 (3H, m), 2.96 (4H, m), 7.16 (2H, t,  $J = 7.2 \text{ Hz}$ ), 7.27 (4H, t,  $J = 7.2 \text{ Hz}$ ), 7.44 (4H, d,  $J = 7.2 \text{ Hz}$ ), 7.57 (2H, d,  $J = 8.5 \text{ Hz}$ ), 7.80 (2H, d,  $J = 8.5 \text{ Hz}$ ). MS ( $\text{ESI}^+$ ) 492, 494 ( $\text{M} + \text{H}^+$ ),  $\text{MS}^2$  ( $m/z$  492): 474, 250, 225, 183,  $\text{MS}^2$  ( $m/z$  494): 476, 250, 227, 185.

*1-[4-(2,2-Difluoroethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butan-1-one*, **12**: 32 % yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.43 (4H, m), 1.92 (3H, m), 2.38 (4H, m), 2.94 (4H, m), 3.17 (2H, td,  $^3J[^{19}\text{F}-^1\text{H}] = 15.1 \text{ Hz}$ ,  $J[^1\text{H}-^1\text{H}] = 4.3 \text{ Hz}$ ), 5.93 (1H, tt,  $^2J[^{19}\text{F}-^1\text{H}] = 56.3 \text{ Hz}$ ,  $J[^1\text{H}-^1\text{H}] = 4.4 \text{ Hz}$ ), 7.15 (2H, t,  $J = 7.3 \text{ Hz}$ ), 7.27 (6H, m), 7.46 (4H, d,  $J = 7.3 \text{ Hz}$ ), 7.91 (2H, d,  $J = 8.1 \text{ Hz}$ ).  $\text{MS}^2$  ( $\text{ESI}$ ) 478 ( $\text{M} + \text{H}^+$ ), 460, 268, 250, 211, 169.

*1-(Benzo[d][1,3]dioxol-5-yl)-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butan-1-one*, **13**: 56 % yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.48 (4H, m), 1.91 (2H, t,  $J = 7.0 \text{ Hz}$ ), 1.96 (2H, m), 2.41 (3H, m), 2.89 (2H, t,  $J = 7.0 \text{ Hz}$ ), 2.97 (2H, m), 6.01 (2H, m), 6.81 (1H, d,  $J = 8.2 \text{ Hz}$ ), 7.15 (2H, t,  $J = 7.4 \text{ Hz}$ ), 7.27 (4H, d,  $J = 7.4 \text{ Hz}$ ), 7.42 (1H, s), 7.45 (4H, d,  $J = 7.4 \text{ Hz}$ ), 7.53 (1H, d,  $J = 8.2 \text{ Hz}$ ).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  458 ( $\text{M} + \text{H}^+$ ), 440, 268, 250, 220, 191, 149.

*N*-[3-(4-{4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-1-oxobutyl}phenyl)ethyl]acetamide, **15**: 62 % yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.41 (4H, m), 1.85 (3H, s), 1.98 (4H, m), 2.44 (3H, m), 2.86 (2H, t,  $J = 6.7$  Hz), 2.96 (4H, m), 3.51 (2H, t,  $J = 6.7$  Hz), 5.51 (1H, bs), 7.15 (2H, t,  $J = 7.3$  Hz), 7.27 (6H, m), 7.42 (4H, d,  $J = 7.3$  Hz), 7.89 (2H, d,  $J = 8.1$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  499 ( $\text{M} + \text{H}^+$ ), 481, 250, 232, 190, 173.

*Diphenyl(1-(4-(4-propylphenyl)butyl)piperidin-4-yl)methanol*, **17**: 30% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.91 (3H, t,  $J = 7.3$  Hz), 1.48-1.64 (10H, m), 1.92 (2H, m), 2.32 (2H, t,  $J = 7.0$  Hz), 2.41 (1H, m), 2.54 (4H, m), 2.95 (2H, m), 7.04 (4H, s), 7.15 (2H, t,  $J = 7.4$  Hz), 7.27 (4H, t,  $J = 7.4$  Hz), 7.46 (4H, d,  $J = 7.4$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  442 ( $\text{M} + \text{H}^+$ ), 424, 250, 173.

*2-(4-{4-[4-(Diphenylmethoxy)piperidin-1-yl]-1-oxobutyl}phenyl)ethyl acetate* (precursor of compound **19**): 61 % yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.68 (2H, m), 1.84 (2H, m), 1.90 (4H, m), 2.00 (3H, s), 2.37 (2H, t,  $J = 6.9$  Hz), 2.72 (2H, m), 2.96 (4H, m), 3.42 (1H, m), 4.28 (2H, t,  $J = 6.9$  Hz), 5.48 (1H, s), 7.27 (12H, m), 7.88 (2H, d,  $J = 8.2$  Hz).

*1-(4-allylphenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one*, **5**: Mp = 219-220°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.63 (4H, m), 2.35 (4H, m), 2.74 (3H, m), 3.07 (2H, m), 3.17 (2H, t,  $J = 6.2$  Hz), 3.42 (2H, d,  $J = 6.6$  Hz), 5.08 (2H, m), 5.94 (1H, m), 7.21 (2H, t,  $J = 7.3$  Hz), 7.28 (6H, m), 7.47 (4H, d,  $J = 7.3$  Hz), 7.85 (2H, d,  $J = 8.2$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  454 ( $\text{M} + \text{H}^+$ ), 436, 268, 250, 187, 145.

*1-(4-*N*-imidazolylphenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one*, **14**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.52 (4H, m), 2.03 (4H, m), 2.51 (3H, m), 3.1 (4H, t,  $J = 5.9$  Hz), 7.3-7.5 (14H, m), 8.01 (1H, s), 8.1 (2H, d,  $J = 8.5$  Hz).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  480 ( $\text{M} + \text{H}^+$ ), 462, 310, 316, 213.

*4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-(2-hydroxyethyl)phenyl)butan-1-one*, **7**: 77 % yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.40 (4H, m), 1.89 (4H, m), 2.35 (3H, m), 2.92 (6H, m), 3.85

(2H, t,  $J = 6.4$  Hz), 7.14 (2H, t,  $J = 7.4$  Hz), 7.27 (6H, m), 7.44 (4H, d,  $J = 7.4$  Hz), 7.90 (2H, d,  $J = 8.0$  Hz). MS<sup>2</sup> (ESI<sup>+</sup>) : m/z 458 (M + H<sup>+</sup>), 440, 422, 268, 250, 191, 149.

*4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-(3-hydroxypropyl)phenyl)butan-1-one*, **8**: : 94 % yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.50 (4H, m), 1.88 (2H, t,  $J = 6.7$  Hz), 1.99 (2H, t,  $J = 6.7$  Hz), 2.11 (2H, m), 2.50 (3H, m), 2.75 (2H, t,  $J = 6.7$  Hz), 2.97 (2H, t,  $J = 6.7$  Hz), 3.02 (2H, m), 3.64 (2H, t,  $J = 6.7$  Hz), 7.15 (2H, t,  $J = 7.0$  Hz), 7.27 (6H, m), 7.45 (4H, d,  $J = 7.0$  Hz), 7.87 (2H, d,  $J = 8.0$  Hz). MS<sup>2</sup> (ESI<sup>+</sup>) : m/z 472 (M + H<sup>+</sup>), 454, 436, 250, 205, 163.

*4-(4-(diphenylmethoxy)piperidin-1-yl)-1-(4-(2-hydroxyethyl)phenyl)butan-1-one*, **19**: 33 % yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.63 (2H, m), 1.92 (4H, m), 2.00 (2H, m), 2.37 (2H, m), 2.73 (2H, m), 2.90 (4H, m), 3.41 (1H, m), 3.87 (2H, t,  $J = 6.5$  Hz), 5.48 (1H, s), 7.19-7.37 (12H, m), 7.89 (2H, d,  $J = 8.2$  Hz). MS<sup>2</sup> (ESI<sup>+</sup>): m/z 458 (M + H<sup>+</sup>), 440, 268, 191, 149.

*4-(4-(diphenylmethoxy)piperidin-1-yl)-1-(4-(2-tertbutyl)phenyl)butan-1-ol*, **18**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.39 (9H, s), 1.77 (2H, m), 1.85-2.00 (4H, m), 2.37 (2H, m), 2.50 (2H, m), 2.73 (2H, m), 2.9 (2H, m), 3.61 (1H, m), 4.71 (1H, m), 5.57 (1H, s), 7.19-7.43 (14H, m). MS<sup>2</sup> (ESI<sup>+</sup>) : m/z 472 (M + H<sup>+</sup>), 455, 167.

*4-[4-(diphenylmethoxy)piperidin-1-yl]-1-(4-vinylphenyl)butan-1-one*, **20**: 71 % yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.67 (2H, m), 1.88 (2H, m), 1.93 (2H, m), 2.19 (2H, m), 2.75 (4H, m), 2.97 (2H, t,  $J = 7.1$  Hz), 3.42 (1H, m), 5.36 (1H, d,  $J = 10.9$  Hz), 5.48 (1H, s), 5.85 (1H, d,  $J = 17.6$  Hz), 6.73 (1H, dd,  $J = 10.9, 17.6$  Hz), 7.30 (10H, m), 7.45 (2H, d,  $J = 8.3$  Hz), 7.91 (2H, d,  $J = 8.3$  Hz). MS<sup>2</sup> (ESI<sup>+</sup>) : m/z 440 (M + H<sup>+</sup>), 278, 268, 173, 167.

*4-[4-(diphenylmethoxy)piperidin-1-yl]-1-[4-(2-thiomethoxy)ethylphenyl]butan-1-one*, **21**: 71 % yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.75 (2H, m), 1.94 (4H, m), 2.15 (3H, s), 2.21 (4H, m), 2.44 (2H, t,  $J = 7.0$  Hz), 3.00 (6H, m), 3.46 (1H, m), 5.54 (1H, s), 7.22-7.39 (12H, m), 7.95 (2H, d,  $J = 8.2$  Hz). MS<sup>2</sup> (ESI<sup>+</sup>): m/z 488 (M + H<sup>+</sup>), 268, 221, 179, 167.

*4-[4-(diphenylmethylene)piperidin-1-yl]-1-[4-tertbutylphenyl]butan-1-one 22*: 70 % yield.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.39 (9H, s), 2.12 (2H,m), 2.63 (4H, t,  $J = 5.5 \text{ Hz}$ ), 2.77 (2H, t,  $J = 6.7 \text{ Hz}$ ), 2.85 (4H, m), 3.12 (2H, t,  $J = 6.7 \text{ Hz}$ ), 7.15 (4H, m), 7.30 (6H, m), 7.49 (2H, d,  $J = 8.5 \text{ Hz}$ ), 7.92 (2H, d,  $J = 8.5 \text{ Hz}$ ).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  452 ( $\text{M} + \text{H}^+$ ), 250, 203, 161.

*1-[4-(2-aminoethyl)phenyl]-4-[4-(diphenylmethylene)piperidin-1-yl]butan-1-one 23*: 60 %

yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.96 (2H, m), 2.36 (4H, t,  $J = 5.5 \text{ Hz}$ ), 2.51 (6H, m), 2.79 (2H, t,  $J = 7.0 \text{ Hz}$ ), 3.00 (6H, m), 7.09 (2H, d,  $J = 8.2 \text{ Hz}$ ), 7.17-7.28 (10H, m), 7.90 (2H, d,  $J = 8.2 \text{ Hz}$ ).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  439 ( $\text{M} + \text{H}^+$ ), 250, 190, 161, 148.

*4-(diphenylmethylene)-1-[4-(4-tertbutylphenyl)but-3-enyl]piperidine hydrochloride 24*: 51

% yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.34 (9H, s), 2.77 (4H, m), 2.92 (2H, m), 3.09 (4H, m), 3.72 (2H, m), 6.10 (1H, dt,  $J = 15.5 \text{ Hz}$ ,  $7.0 \text{ Hz}$ ), 6.54 (1H, d,  $J = 15.5 \text{ Hz}$ ), 7.12 (4H, m), 7.30 (8H, m), 7.92 (2H, d,  $J = 8.5 \text{ Hz}$ ).  $\text{MS}^2$  ( $\text{ESI}^+$ ):  $m/z$  436 ( $\text{M} + \text{H}^+$ ), 262, 250, 188. The *trans* configuration of the  $\text{CH}=\text{CH}$  bond is indicated by the large value of the coupling constant of the vinylic protons ( $J = 15.5 \text{ Hz}$ ).

**2) Figure: Effects of the presence of compound 4 (A) or of GSH (B) on the rate of CYP2J2 inactivation by 13.** Loss of P450 2J2 activity after NADPH-dependent oxidation of 5  $\mu\text{M}$  compound **13** was evaluated as a function of time in the presence ( $\Delta$ ) or absence ( $\bullet$ ) of 50  $\mu\text{M}$  **4** (or 5 mM GSH). Control incubations ( $\blacktriangle$ ) without compound **13** were also run in parallel. Values are means  $\pm$  SD of three independent experiments.