Discovery of small molecule PDI inhibitor that inhibits reduction of HIV-1 envelope glycoprotein gp120

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Supplementary Methods:

Compound Characterization: ^{1}H NMR spectra were recorded on a JEOL JNM-ECP-500 (500 MHz) spectrometer in $CDCl_3$ with tetramethylsilane (0 ppm) as internal standard. The following abbreviations were used to explain the multiplicities: s, single; d, doublet; t, triplet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a JEOL JNM-ECP-500 (125 MHz) spectrometer in $CDCl_3$ as solvent and internal standard (77.0 ppm).

Compound 1

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.05 (dd, *J* = 12.8, 6.9 Hz, 1 H), 1.20-1.35 (m, 3H), 1.64 (m, 1H), 1.70 (bs, 3H), 1.72 (d, *J* = 1.4 Hz, 3H), 2.14 (bdd, *J* = 12.8, 5.0 Hz, 1H), 2.37 (bs, 1H), 2.50-2.58 (m, 2H), 4.22 (d, *J* = 10.1 Hz, 1H), 5.10 (dd, *J* = 8.2, 7.8 Hz, 1 H), 5.57 (bdd, *J* = 10.1, 3.2 Hz, 1H), 5.58 (bd, *J* = 10.1 Hz, 1H), 6.85 (bd, *J* = 8.7 Hz, 1H), 7.94 (bd, *J* = 8.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 18.4, 23.0, 23.1, 23.1, 29.8, 36.4, 36.8, 37.6, 70.7, 72.6, 115.4, 118.9, 122.0, 129.2, 131.9, 135.7, 140.1, 160.6, 166.2.

Compound 2

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.05 (dd, *J* = 12.9, 6.9 Hz, 1 H), 1.20-1.33 (m, 3H), 1.55-1.70 (m, 1H), 1.70 (bs, 3H), 1.72 (d, *J* = 1.4 Hz, 3H), 2.14 (bdd, *J* = 12.6, 5.2 Hz, 1H), 2.30 (bs, 1H), 2.50-2.59 (m, 2H), 3.86 (s, 3 H), 4.22 (d, *J* = 10.1 Hz, 1H), 5.10 (dd, *J* = 8.2, 7.8 Hz, 1 H), 5.58 (bd, *J* = 10.1 Hz, 1H), 5.59 (bdd, *J* = 10.1, 3.2 Hz, 1H), 6.92 (bd, *J* = 8.7 Hz, 1H), 7.99 (bd, *J* = 8.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 18.4, 23.0, 23.0, 23.1, 29.8, 36.4, 36.8, 37.7, 55.4, 70.1, 72.6, 113.6, 118.9, 122.7, 130.0, 131.6, 134.9, 140.1, 163.4, 165.8.

Compound 3

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (s, 3H), 0.97 (s, 3H), 1.15 (dd, *J* = 13.3, 6.9 Hz, 1 H), 1.20-1.40 (m, 3H), 1. 60-1.70 (m, 1H), 1.79 (bs, 3H), 1.80 (d, *J* = 1.4 Hz, 3H), 2.08 (s, 3H), 2.18 (bdd, *J* = 12.8, 5.2 Hz, 1H), 2.45 (ddd, *J* = 11.9, 11.9, 9.2 Hz, 1H), 2.55-2.65 (m, 1H), 5.20 (dd, *J* = 8.2, 7.8

Hz, 1 H), 5.46 (d, *J* = 10.1 Hz, 1H), 5.51 (bd, *J* = 10.1 Hz, 1H), 5.73 (bdd, *J* = 11.9, 4.1 Hz, 1H), 6.81 (bd, *J* = 8.7 Hz, 1H), 7.91 (bd, *J* = 8.7 Hz, 1H).

Compound 4

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.05 (dd, *J* = 13.3, 6.9 Hz, 1 H), 1.20-1.35 (m, 3H), 1. 60-1.70 (m, 1H), 1.70 (bs, 3H), 1.72 (d, *J* = 1.4 Hz, 3H), 2.14 (bdd, *J* = 12.8, 5.2 Hz, 1H), 2.23 (bs, 1H), 2.33 (s, 3H), 2.50-2.60 (m, 2H), 4.21 (d, *J* = 10.1 Hz, 1H), 5.10 (dd, *J* = 8.2, 7.8 Hz, 1 H), 5.59 (bd, *J* = 10.1 Hz, 1H), 5.59 (bdd, *J* = 10.5, 4.1 Hz, 1H), 7.17 (bd, *J* = 8.7 Hz, 1H), 8.06 (bd, *J* = 8.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3, 18.5, 21.1, 23.0, 23.0, 23.1, 29.8, 36.5, 36.8, 37.6, 70.1, 73.1, 118.7, 121.6, 127.8, 130.2, 131.2, 134.6, 140.2, 154.4, 165.3, 168.8.

Compound 5

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (s, 3H), 0.97 (s, 3H), 1.14 (dd, *J* = 13.0, 6.9 Hz, 1 H), 1.20-1.40 (m, 3H), 1. 60-1.70 (m, 1H), 1.79 (bs, 3H), 1.80 (d, *J* = 1.4 Hz, 3H), 2.06 (s, 3H), 2.18 (bdd, *J* = 12.6, 5.2 Hz, 1H), 2.32 (s, 3H), 2.40-2.65 (m, 2H), 5.19 (dd, *J* = 8.2, 7.8 Hz, 1 H), 5.43 (d, *J* = 10.1 Hz, 1H), 5.51 (bd, *J* = 10.1 Hz, 1H), 5.77 (bdd, *J* = 11.4, 4.1 Hz, 1H), 7.14 (bd, *J* = 8.7 Hz, 1H), 8.06 (bd, *J* = 8.7 Hz, 1H).

Compound 6

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.00 (s, 3H), 1.05 (dd, *J* = 13.3, 6.9 Hz, 1 H), 1.20-1.35 (m, 3H), 1.60-1.68 (m, 1H), 1.71 (bs, 3H), 1.74 (d, *J* = 1.4 Hz, 3H), 2.15 (bdd, *J* = 12.8, 5.5 Hz, 1H), 2.23 (bs, 1H), 2.52-2.62 (m, 2H), 4.22 (d, *J* = 10.1 Hz, 1H), 5.11 (dd, *J* = 8.2, 7.9 Hz, 1 H), 5.60 (bd, *J* = 10.1 Hz, 1H), 5.61 (dd, *J* = 10.5, 5.5 Hz, 1H), 7.44 (dd, *J* = 7.7, 7.3 Hz, 1H), 7.57 (tt, *J* = 7.3, 1.4 Hz, 1H), 8.04 (dd, *J* = 7.7, 1.4 Hz, 1H).

Compound 7

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.04 (dd, *J* = 13.3, 6.9 Hz, 1 H), 1.25-1.35 (m, 3H), 1.64 (m, 1H), 1.71 (bs, 3H), 1.73 (d, *J* = 1.4 Hz, 3H), 2.14 (bdd, *J* = 12.8, 5.0 Hz, 1H), 2.22 (bs, 1H), 2.50-2.60 (m, 2H), 4.21 (d, *J* = 10.1 Hz, 1H), 5.10 (dd, *J* = 8.2, 7.8 Hz, 1 H), 5.59

(bdd, *J* = 10.5, 4.6 Hz, 1H), 5.60 (bd, *J* = 10.1 Hz, 1H), 7.11 (dd, *J* = 8.7, 8.7 Hz, 1H), 8.05 (dd, *J* = 8.7, 6.4 Hz, 1H).

Compound 8

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20-1.48 (m, 10 H), 1.75 (tt, *J* = 6.9, 6.9 Hz, 2H), 4.28 (t, *J* = 6.9 Hz, 2H), 5.61 (bs, 1H), 6.87 (bd, *J* = 8.7 Hz, 1H), 7.96 (bd, *J* = 8.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.6, 26.0, 28.7, 29.2, 29.3, 31.8, 65.0, 115.1,123.1, 131.9, 159.7, 166.6.

Compound 9

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50-2.00 (m, 14 H), 5.17 (m, 1H), 5.31 (bs, 1H), 6.85 (bd, *J* = 8.7 Hz, 1H), 7.95 (bd, *J* = 8.7 Hz, 1H).

Compound 10

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20-1.90 (m, 22 H), 5.22 (m, 1H), 6.83 (bd, *J* = 8.7 Hz, 1H), 7.93 (bd, *J* = 8.7 Hz, 1H).

Compound 11

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 1.10-2.40 (m, 9 H), 4.89 (ddd, *J* = 11.0, 11.0, 4.6 Hz, 1H), 6.85 (bd, *J* = 8.7 Hz, 1H), 7.95 (bd, *J* = 8.7 Hz, 1H).

Compound 12

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (s, 3H), 0.93 (s, 3H), 1.07 (dd, *J* = 14.2, 8.2 Hz, 1 H), 1.10-1.60 (m, 1H), 1.24 (ddd, *J* = 14.2, 9.6, 8.0 Hz, 1H), 1.50 (ddd, *J* = 12.8, 12.8, 1.8 Hz, 1H), 1.54-1.64 (m, 1H), 1.65 (bs, 3H), 1.79 (d, *J* = 1.4 Hz, 3H), 2.08 (bdd, *J* = 12.8, 4.6 Hz, 1H), 2.23 (bs, 1H), 2.31 (ddd, *J* = 12.4, 11.0, 8.7 Hz, 1H), 2.38 (ddd, *J* = 12.4, 7.8, 4.1 Hz, 1H), 4.00 (d, *J* = 10.1 Hz, 1H), 4.50 (dd, *J* = 11.0, 4.1 Hz, 1H), 5.03 (dd, *J* = 8.7, 7.8 Hz, 1 H), 5.42 (d, *J* = 10.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 18.3, 23.1, 23.2, 23.2, 33.3, 36.5, 37.1, 37.3, 69.9, 70.2, 119.9, 127.3, 138.6, 140.5.

Compound 13 (1:1 stereoisomers)

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (dd, *J* = 13.3, 10.5 Hz, 1H), 0.93 (s, 3H), 0.96 (s, 3H), 1.04 (s, 3H), 1.05 (s, 3H), 1.20-1.85 (m, 11H), 1.33 (s, 3H), 1.42 (s, 3H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.94 (ddd, *J* = 12.4, 11.0, 11.5 Hz, 1H), 2.10 (dd, *J* = 13.7, 8.7 Hz, 1H), 2.44 (ddd, *J* = 12.4, 3.7, 2.0 Hz, 1H), 2.62 (bs, 1H), 2.65 (ddd, *J* = 12.4, 12.4, 3.7 Hz, 1H), 2.74 (dd, *J* = 10.5, 4.1 Hz, 1H), 2.92 (bs, 1H), 3.04 (dd, *J* = 10.5, 3.7 Hz, 1H), 4.65 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 10.5 Hz, 1H), 5.82 (dd, *J* = 12.4, 3.7 Hz, 1H), 6.00 (dd, *J* = 12.4, 2.0 Hz, 1 H), 6.55 (bs, 1H)), 6.85 (bd, *J* = 8.7 Hz, 2H), 7.88 (bd, *J* = 8.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 16.8, 17.4, 17.7, 19.1, 21.4, 21.5, 21.6, 22.9, 24.0, 30.1, 30.7, 36.7, 36.8, 37.0, 37.5, 37.7, 39.3, 58.0, 59.0, 60.5, 60.8, 63.2, 69.6, 69.7, 70.3, 71.0, 115.4, 115.4, 122.1, 122.1, 131.0, 131.5, 132.0, 132.0, 134.5, 160.5, 160.5, 165.8, 165.8.

Compound 14

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.01 (s, 3H), 1.03 (dd, *J* = 12.9, 6.9 Hz, 1H), 1.20-1.46 (m, 3H), 1.55 (s, 3H), 1.65 (m, 1H), 1.78 (s, 3H), 2.12 (bs, 1H), 2.16 (dd, *J* = 14.3, 4.6 Hz, 3H), 2.46 (ddd, *J* = 13.2, 11.5, 9.2 Hz, 1H), 2.73 (ddd, *J* = 13.2, 7.4, 4.6 Hz, 1H), 2.98 (d, *J* = 8.0 Hz, 1H), 3.39 (d, *J* = 8.0 Hz, 1H), 4.84 (dd, *J* = 11.5, 4.6 Hz, 1H), 5.19 (dd, *J* = 9.2, 7.4 Hz, 1H), 6.86 (bd, *J* = 8.6 Hz, 2H), 7.95 (bd, *J* = 8.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 18.0, 18.2, 21.7, 23.0, 23.6, 30.3, 35.6, 36.3, 37.2, 65.2, 65.9, 69.3, 74.6, 115.2, 116.8, 122.5, 132.0, 139.6, 165.4, 165.8.

Compound 15

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.03 (s, 3H), 1.20-2.20 (m, 6H), 1.44 (s, 3H), 1.61 (s, 3H), 2.38-2.50 (m, 2H), 2.91 (dd, *J* = 10.9, 4.0 Hz, 3H), 3.09 (d, *J* = 8.5 Hz, 1H), 3.56 (d, *J* = 8.5 Hz, 1H), 5.00 (dd, *J* = 12.0, 4.0 Hz, 1H), 6.87 (bd, *J* = 8.7 Hz, 2H), 7.97 (bd, *J* = 8.7 Hz, 2H).

Compound 16

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.04 (s, 3H), 1.10-1.80 (m, 5H), 1.23 (s, 3H), 1.85 (d, *J* = 1.1 Hz, 3H), 2.08 (ddd, *J* = 14.3, 10.9, 5.2 Hz, 1H), 2.30 (ddd, *J* = 14.3, 11.5, 1.7 Hz, 1H), 2.53

(bs, 1H), 3.68 (d, *J* = 10.9 Hz, 1H), 4.63 (d, *J* = 10.3 Hz, 1H), 5.63 (dd, *J* = 10.3, 1.1 Hz, 1 H), 5.85 (bs, 1H), 5.91 (dd, *J* = 11.5, 5.2 Hz, 1H), 6.84 (bd, *J* = 8.7 Hz, 1H), 7.87 (bd, *J* = 8.7 Hz, 1H).

Compound 17

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.06 (s, 3H), 1.10-2.40 (m, 8H), 1.13 (s, 3H), 1.84 (d, *J* = 1.1 Hz, 3H), 4.20 (m, 1H), 4.64 (d, *J* = 10.3 Hz, 1H), 5.46 (dd, *J* = 10.3, 1.1 Hz, 1 H), 5.92 (dd, *J* = 5.7, 2.9 Hz, 1H), 6.85 (bd, *J* = 8.6 Hz, 1H), 7.91 (bd, *J* = 8.6 Hz, 1H).

MCF-7 Proliferation: Human breast cancer MCF-7 (ER-positive) cells were cultured in phenol red-free RPMI (Sigma) supplemented with 5% dextran-coated charcoal-stripped FBS (Sigma) for 48 hours before plating. MCF-7 cells (1.5×10^4) were plated in twenty-four well plate. Twenty-four hours later, cells were treated with DMSO, estradiol (10 nM), juniferdin (100 nM), compound 13 (100 nM) and tamoxifen (10 μM) and cells were counted (day 0). Forty-eight and ninety-six hours later cells were again counted (day 2 and day 4).

Cell Viability: The HeLa, HepG2, HL-60, HT1080 and K562 cell lines, grown in 96-well plates for 24 hours, were incubated with juniferdin and compound **13** for an additional 24 hours. Cell viability was assessed using Wst-8 (Nacalai Tesque) according to the manufacturer's instructions.

Measurement of Lysozyme Reactivation: Lysozyme (15 mg) was reduced and denatured by incubating in 5 ml of 6 M guanidine HCl in 0.1 M Tris-acetate (pH8.0), 2 mM EDTA and 0.15 M DTT. The reduced and denatured lysozyme was separated from DTT and guanidine-HCl using Sephadex G-25 equilibrated with 0.1% (v/v) acetic acid. PDI mediated lysozyme reactivation was measured according to Puig et al. (J. Biol. Chem. 1994 269: 7764-7771), with slight modifications. After desalting, reduced and denatured lysozyme was diluted to a final concentration of 1 μM in a 100 μl volume containing redox buffer (5 mM GSH and 0.5 mM GSSG), 1 μM PDI (in 100 mM HEPES, 20 mM NaCl, 2 mM EDTA and 5 mM $MgCl_2$, pH 7.0) and 0.5 mg/ml *Micrococcus lysodeikticus* cell wall suspension (in 0.06 M potassium phosphate, 0.1% NaCl, pH 6.2). Lysozyme activity was measured by following the decrease in absorbance at 620 nm at room temperature. Lysozyme was bought from Seikagaku Bioscience Corporation and *Micrococcus lysodeikticus* lyophilized cells were bought from Sigma.

Supplementary TABLE 1: Structure of juniferdin and derivative 2-11.

Supplementary TABLE 2: Comparison of inhibitory potency on PDI activity.

Supplementary TABLE 3: Effect of juniferdin and compound 13 on the viability of cell lines.

Supplementary Scheme 1: General synthetic route for the generation of juniferdin derivatives. Reagents and conditions. (a) Ac_2O, pyridine, CH_2Cl_2, rt; (b) $TMSCHN_2$, benzene-MeOH, rt; (c) 1N NaOH, THF, 60°C; (d) mcpba, CH_2Cl_2, rt; (e) t-BuOOH, $VO(acac)_2$, benzene, reflux; (f) OsO_4, NMO, acetone-H_2O, rt; (g) pyridine, CH_2Cl_2, rt; (h) EDCI, DMAP, CH_2Cl_2-THF, rt.

Supplementary Figure Legends

Supplementary Figure 1: Inhibitory potency of 17β-estradiol, estrone and juniferdin. Inhibition of PDI reductase activity was measured by the insulin reduction assay. a) Comparison of PDI reductase activity inhibition by 17β-estradiol and juniferdin. b) Comparison of PDI reductase activity inhibition by estrone and juniferdin

Supplementary Figure 2: Effect of estradiol, juniferdin, compound 13 and tamoxifen on the proliferation of MCF-7. MCF-7 cells were cultured in phenol red-free RPMI supplemented with 5% dextran-coated charcoal-stripped FBS for 48 hours before plating. Later, 1.5×10^4 MCF-7 cells were plated in twenty-four well plate. Twenty-four hours later, cells were treated with DMSO, 17β-estradiol (10 nM), juniferdin (100 nM), compound 13 (100 nM) and tamoxifen (10 μM) and cells were counted according the above mentioned time period.

Supplementary Figure 3: Measurement of PDI oxidase activity by lysozyme renaturation. Reduced and denatured lysozyme (1 μM) was added in a 100 μl volume containing redox buffer (5 mM GSH and 0.5 mM GSSG), 1 μM PDI (in 100 mM HEPES, 20 mM NaCl, 2 mM EDTA and 5 mM $MgCl_2$, pH 7.0) and 0.5 mg/ml *Micrococcus lysodeikticus* cell wall suspension in the presence or absence of juniferdin.

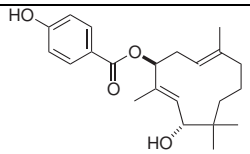
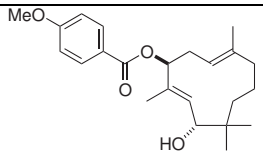
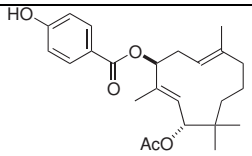
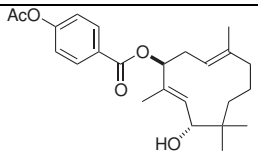
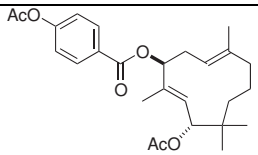
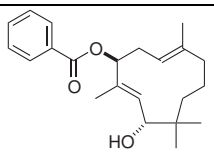
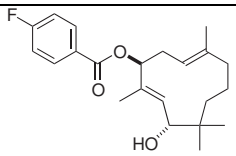
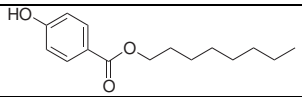
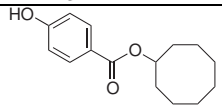
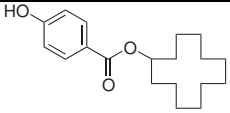
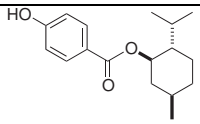
Supplementary Figure 4: Effect of juniferdin (10 μM) on the reductive activity of thioredoxin, as measured by the insulin turbidometry assay.

Supplementary Figure 5: Domain architecture of human PDI. Numbers correspond to full length human PDI. Human PDI has four domains, a, b, b´ and a´, followed by a C-terminal

extension that harbors the ER retention signal (KDEL). The a and a´ domains contain one catalytically active CGHC motif, while the b and b´domains are redox inactive.

Supplementary Figure 6: Schematic diagram of PDI-inhibitor mediated blocking of HIV-1 fusion. PDI has separate binding sites for CD4 and HIV-1 envelope glycoprotein gp120. PDI stabilizes the binding of HIV-1 to CD4, followed by the subsequent reduction of at least two of the nine disulfide bonds of gp120. This triggers conformational changes in gp120, followed by the transformation of gp41 that initiates the fusion of HIV-1 and host cells. Juniferdin and compound **13** inhibit the PDI mediated reduction of HIV-1 glycoprotein gp120.

Supplementary TABLE 1: Structure of juniferdin and derivative 2-11

Compound	Structure
1: Juniferdin	
2	
3: Juniferidin	
4	
5	
6	
7	
8	
9	
10	
11	

Supplementary Table 2: Comparison of inhibitory potency on PDI activity

Compound	Tested method	PDI activity inhibition (%)	Concentration	Ref.
Bacitracin	Insulin-reduction	95	3 mM	[a,b]
DTNB	Insulin-reduction	100	1 mM	[a,b]
pCMBS	Insulin-reduction	100	1 mM	[a]
Diethylstilbesterol	Insulin-reduction	40-60	1 µM	[c]
Estradiol	Insulin-reduction	40-60	1 µM	[c]
Juniferdin	Insulin-reduction	98	10 µM	This paper
Compound 13	Insulin-reduction	97	10 µM	This paper

[a] Mandel, R., Ryser, H. J., Ghani, F., Wu, M., and Peak, D. (1993) Inhibition of a reductive function of the plasma membrane by bacitracin and antibodies against protein disulfide-isomerase, *Proc Natl Acad Sci U S A 90*, 4112-4116.

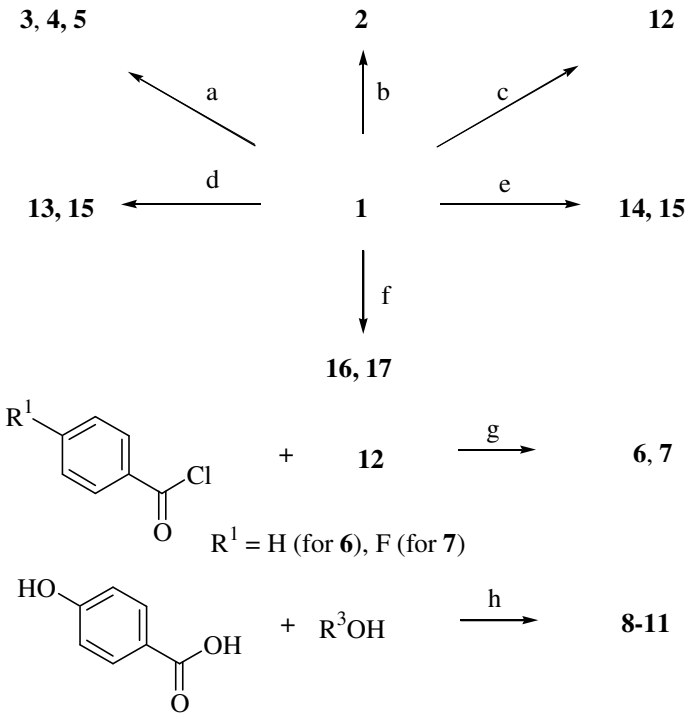
[b] Ryser, H. J., Levy, E. M., Mandel, R., and DiSciullo, G. J. (1994) Inhibition of human immunodeficiency virus infection by agents that interfere with thiol-disulfide interchange upon virus-receptor interaction, *Proc Natl Acad Sci U S A 91*, 4559-4563.

[c] Tsibris, J. C., Hunt, L. T., Ballejo, G., Barker, W. C., Toney, L. J., and Spellacy, W. N. (1989) Selective inhibition of protein disulfide isomerase by estrogens, *J Biol Chem 264*, 13967-13970.

Supplementary TABLE 3: Effect of juniferdin and compound 13 on the viability of cell lines

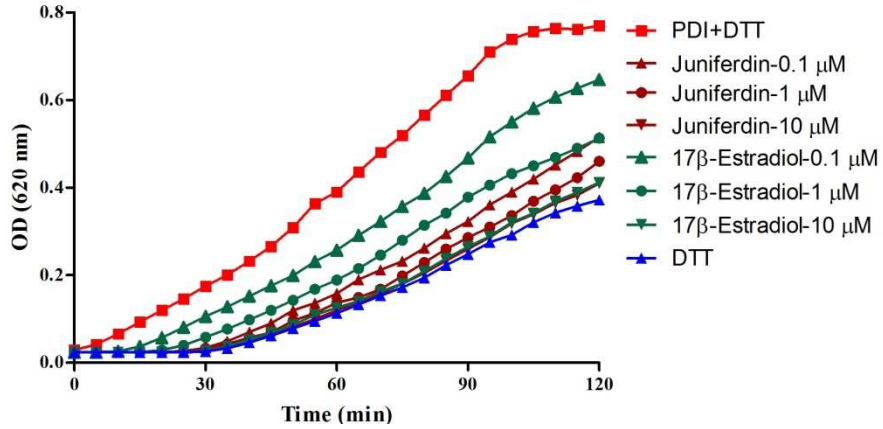
	IC_{50} (µM)	
Cell line	**Juniferdin**	**Compound 13**
HeLa	4	>10
HepG2	3.3	8
HL-60	>10	>10
HT1080	5.3	>10
K562	5.8	>10

Supplementary Scheme 1: General synthetic route for the generation of juniferdin derivatives.

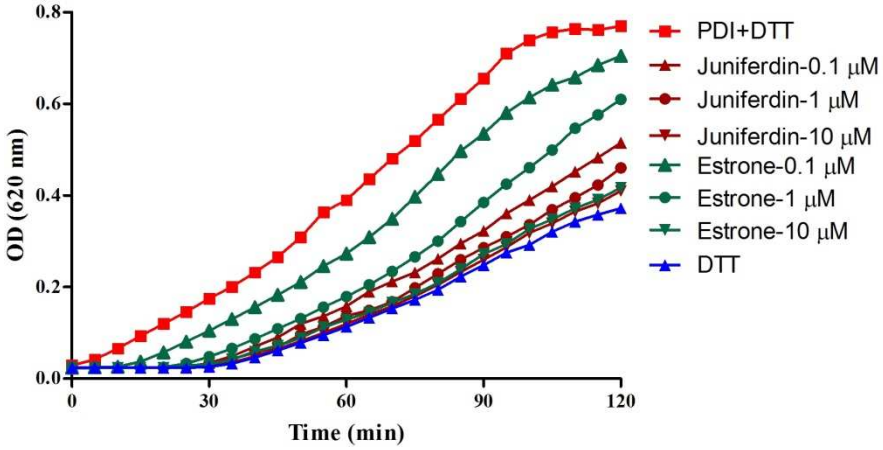


Supplementary Figure 1

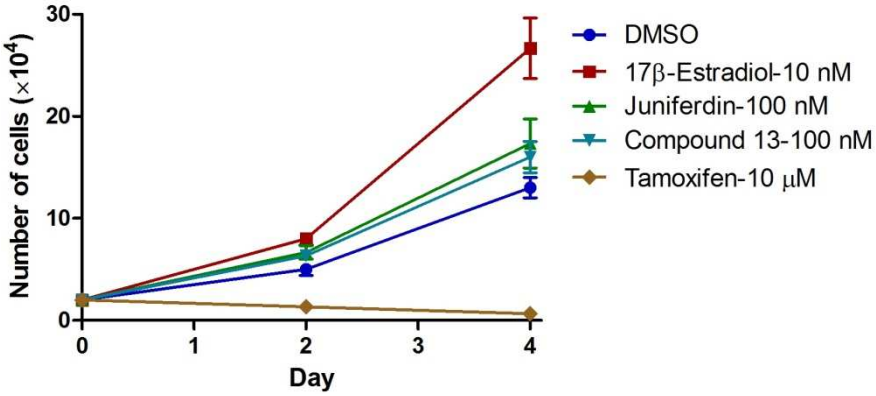
a



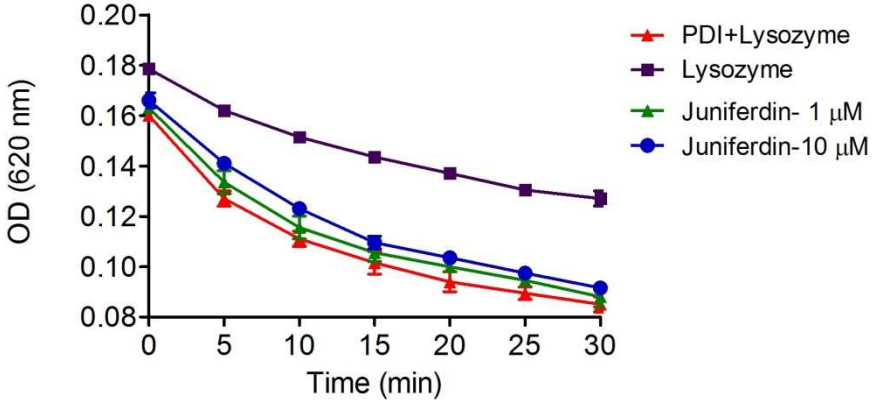
b



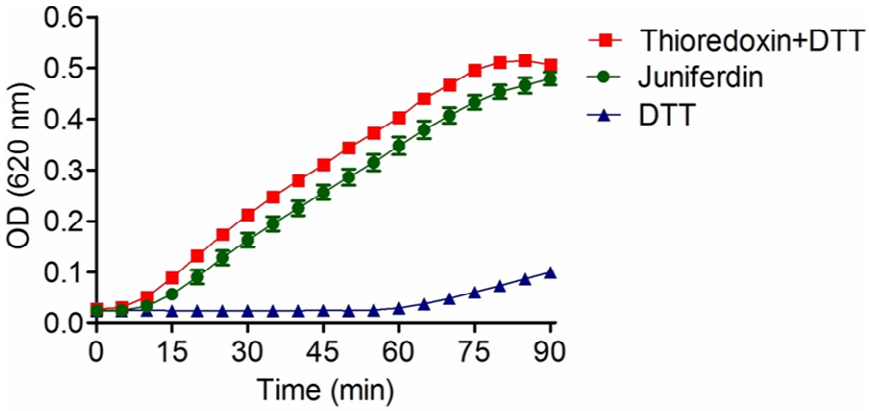
Supplementary Figure 2



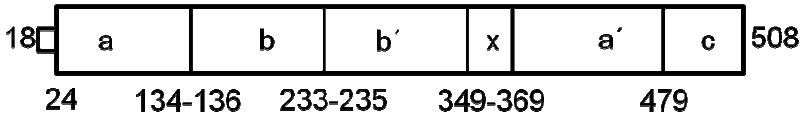
Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6