Electronic Supplementary Material (ESI) for Chemical Science.

Supplementary Information

A new generation of ferrociphenols leads to a great diversity of reactive metabolites, and exhibits remarkable antiproliferative properties

Yong Wang, Patrick M. Dansette, Pascal Pigeon, Siden Top, Michael J. McGlinchey, Daniel Mansuy,* and Gérard Jaouen**

Supplementary Methods

General Synthetic Methods. All reagents and solvents were obtained from commercial suppliers. Acetone was dried over 4 Å molecular sieves. Thin layer chromatography (TLC) was performed on silica gel 60 GF_{254}. Column chromatography was performed on silica gel Merck 60 (40-63 μm). All NMR experiments (^{1}H, ^{13}C) were carried out at room temperature on Bruker 300 and 400 NMR spectrometers, and chemical shifts (δ) are reported in ppm relative to the referenced solvent; s, d, t and q were used for singlet, doublet, triplet, and quartet, respectively. Mass spectra (MS) were obtained on a Focus/DSQII spectrometer for both electron impact (EI) and chemical ionization (CI) methods, and an API 3000 PE SciexApplied Biosystems spectrometer for the electrospray ionization (ESI) method. HRMS measurements were performed on a Thermo Fischer LTQ-Orbitrap XL apparatus equipped with an electrospray source by IPCM (UMR 8232). Elemental analyses were performed by the microanalysis service of ICSN (Gif sur Yvette, France). Ferrociphenols **3a** and **3b**, and corresponding quinone methides, **4a** and **4b**, were prepared by previously described procedures.[1] All other products including enzymes were from Sigma-Aldrich (St. Quentin Fallavier, France). Ag_2O was prepared according the literature procedure. [2]

Reaction of QM 4b under acid conditions

With 1N HCl. Freshly made Ag_2O (0.22g, 0.9 mmol) was added to a solution of 4,4'-(5-hydroxy-2-ferrocenylpent-1-ene-1,1-diyl)diphenol **3b** (0.1 g, 0.23 mmol) in 6 ml of acetone. The dark grey mixture changed to become a dark red suspension about 5 minutes later. The reaction was monitored by TLC until complete conversion of the starting material (20 minutes). Filtration was followed by adding 5 drops of 1N HCl aqueous solution, the red suspension became orange and clear immediately. The solution was diluted with ethyl acetate and washed twice with water, the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give 6 compounds. **4,4'-(hydroxy(2-ferrocenyltetrahydrofuran-2-yl)methylene)diphenol (9b)** as a brown solid 20 mg, yield 18%. ^{1}H NMR (300 MHz, Acetone-d_6) δ = 1.75 (m, 1H; CH_2), 2.60 (m, 2H; CH_2), 3.51 (s, 1H; OH), 3.93 (m, 2H; CH_2), 4.00 (s, 1H; CH_2), 4.03 (m, 2H; C_5H_4), 4.10 (s, 1H; C_5H_4), 4.12(m, 5H; Cp), 4.19 (s, 1H;

C_5H_4), 6.59 (d, J = 8.9 Hz, 2H; C_6H_4), 6.69 (d, J = 8.9 Hz, 2H; C_6H_4), 7.51 (d, J = 8.8 Hz, 2H; C_6H_4), 7.58 (d, J = 8.9 Hz, 2H; C_6H_4), 7.99 (s, 1H; OH), 8.11 (s, 1H; OH). ^{13}C NMR (75 MHz, acetone-d_6) δ = 26.8 (CH_2), 38.2 (CH_2), 67.1 (CH; C_5H_4), 68.1 (CH; C_5H_4), 68.6 (CH; C_5H_4), 69.4 (5 CH; Cp), 70.2 (CH; C_5H_4), 70.4 (OCH_2), 80.6 (C), 91.9 (C), 97.0 (C), 114.4 (4 CH; C_6H_4), 129.8 (4 CH; C_6H_4), 136.6 (C; C_6H_4), 138.7 (C; C_6H_4), 156.3 (C; C_6H_4), 156.5 (C); MS-CI (NH_3) *m/z*: 471 $(M+H)^+$. HRMS calcd for $C_{27}H_{26}FeO_4$ $(M)^+$: 470.1180, found: 470.1183. Anal. Calcd for $C_{27}H_{26}FeO_4(H_2O)_{0.6}$: C, 67.40; H, 5.70. Found: C, 67.48; H, 5.94. **4,4'-(3-ferrocenyl-5,6-dihydro-2H-pyran-2,2-diyl)diphenol (5b)** as a brown solid 10 mg, yield 10%. ^{1}H NMR (300 MHz, acetone-d_6) δ = 2.38 (q, J = 5.4 Hz, 2H; CH_2), 3.50 (t, J = 5.7 Hz, 2H; OCH_2), 3.83 (s, 2H; C_5H_4), 3.97 (s, 2H; C_5H_4), 4.03 – 4.08 (m, 5H; Cp), 6.57 (s, 1H; CH=C), 6.75 (d, J = 8.7 Hz, 4H; C_6H_4), 7.20 (d, J = 8.7 Hz, 4H; C_6H_4), 8.32 (s, 2H; OH). ^{13}C NMR (75 MHz, acetone-d_6) δ = 27.0 (CH_2), 59.2 (OCH_2), 68.2 (2 CH; C_5H_4),70.5 (2 CH; C_5H_4),70.9 (5 CH; Cp), 84.1 (C; C-O), 86.2 (C; Fc_{ipso}), 114.7 (4 CH; C_6H_4), 125.7 (CH; CH=C), 131.9 (4 CH; C_6H_4), 136.2 (2 C; C_6H_4), 141.5 (C; CH=C), 157.4 (2 C; C_6H_4). MS-EI *m/z*: 452 $(M)^+$. HRMS calcd for $C_{27}H_{24}FeO_3$ $(M)^+$: 452.1075, found: 452.1090. Anal. Calcd for $C_{27}H_{24}FeO_3(H_2O)_{0.5}$: C, 70.29; H, 5.46. Found: C, 70.27; H, 5.89.

5-hydroxy-1,1-bis(4-hydroxyphenyl)-1-ferrocenylpentan-2-one(6b) as a brown solid 30 mg, yield 28%. ^{1}H NMR (300 MHz, acetone-d_6) δ = 1.81 (m, 2H; CH_2), 2.82 – 2.90 (m, 2H; CH_2), 3.55 (m, 3H; OH and OCH_2), 3.85 (s, 2H; C_5H_4), 4.14 (s, 5H; Cp), 4.25 (s, 2H; C_5H_4), 6.77 (d, J = 8.8 Hz, 4H; C_6H_4), 6.92 (d, J = 8.8 Hz, 4H; C_6H_4), 8.37 (s, 2H; OH). ^{13}C NMR (75 MHz, acetone-d_6) δ = 29.0 (CH_2), 38.8 (CH_2), 61.9 (OCH_2), 66.3 (C), 68.7 (2 CH; C_5H_4), 70.2 (5 CH; Cp), 71.6 (2 CH; C_5H_4), 92.2 (C; Fc_{ipso}), 115.0 (4 CH; C_6H_4), 131.8 (4 CH; C_6H_4), 136.0 (2 C; C_6H_4), 157.0 (2 C; C_6H_4), 208.6 (C=O). MS-EI *m/z*: 470 $(M)^+$. HRMS calcd for $C_{27}H_{26}FeO_4$ $(M)^+$: 470.1180, found: 470.1198. Anal. Calcd for $C_{27}H_{26}FeO_4(H_2O)_{0.5}$: C, 67.65; H, 5.68. Found: C, 67.68; H, 5.82. **4-hydroxy-1-ferrocenylbutan-1-one (7)** as a brown solid 14 mg, yield 25%. ^{1}H NMR (300 MHz, acetone-d_6) δ = 1.81– 1.93 (m, 2H; CH_2), 2.86 (m, 2H; CH_2), 3.62 (m, 3H; OH and OCH_2), 4.22 (s, 5H; Cp), 4.50 – 4.54 (m, 2H; C_5H_4), 4.78 – 4.82(m, 2H; C_5H_4). ^{13}C NMR (75 MHz, acetone-d_6) δ = 28.2 (CH_2), 36.5 (CH_2), 61.9 (OCH_2), 70.0 (2 CH; C_5H_4), 70.5 (5 CH; Cp), 72.7 (2 CH; C_5H_4), 80. 6 (C; Fc_{ipso}), 203.75 (C=O). **bis(4-hydroxyphenyl)methanone (8b)** as a brown solid 10 mg, yield 23%. ^{1}H NMR (300 MHz, acetone-d_6) δ

= 6.95 (d, J = 8.6 Hz, 4H; C_6H_4), 7.68 (d, J = 8.6 Hz, 4H; C_6H_4), 9.17 (s, 2H; OH). ^{13}C NMR (75 MHz, acetone-d_6) δ = 115.8 (4 CH; C_6H_4), 130.8 (2 C; C_6H_4), 133.0 (4 CH; C_6H_4), 162.0 (2 C; C_6H_4), 194.0 (C=O). **4,4'-(2-(dihydrofuran-2-yl)-2-ferrocenylethene-1,1-diyl)diphenol (10b)** as a brown solid 20 mg, yield 18%. ^{1}H NMR (400 MHz, Acetone-d_6) δ = 2.73 (td, J = 2.4, 9.4Hz, 2H; CH_2), 3.95 (s, 2H; C_5H_4), 4.15 (s, 2H; C_5H_4),4.21 (s, 5H; Cp), 4.51 (t, J = 9.4Hz, 2H; CH_2), 4.55 (t, J = 2.4Hz, 1H; CH),6.70 (d, J = 8.8Hz, 2H; C_6H_4), 6.97 (d, J = 8.8Hz, 2H; C_6H_4), 8.19 (s, 2H; 2OH). ^{13}C NMR (100 MHz, acetone-d_6) δ = 30.2 (CH_2), 67.8 (2 CH; C_5H_4), 69.9 (5 CH; Cp), 70.9 (CH_2), 71.5 (2 CH; C_5H_4),96.5 (C), 99.7 (CH), 114.6 (4 CH; C_6H_4), 131.2 (4 CH; C_6H_4), 138.0 (2 C), 156.7 (2 C), 165.4 (2 C); MS-ESI *m/z*: 452 $(M)^+$. HRMS calcd for $C_{27}H_{24}FeO_3$ $(M)^+$: 452.1075, found: 452.1070. Anal. Calcd for $C_{27}H_{24}FeO_3(H_2O)_{0.4}$: C, 70.57; H, 5.44. Found: C, 70.84; H, 5.68.

With 1N HCl-Et_2O. After the complete conversion of the starting material to quinone methide **4b** (20 minutes), filtration was followed by adding 5 drops of HCl-Et_2O whereupon the red suspension became orange and clear immediately. The solution was diluted with ethyl acetate and washed twice with water, the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give 2 major compounds **3b-A** (yield: 35%) and **3b-B** (yield: 47%).

Reaction of QM 4b with methanol

Freshly made **4b** (100 mg, 0.22 mmol) was dissolved in methanol and the solution was stirred for approximately 2 hrs. The solvent was removed and the residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give **14b** (70 mg, yield: 65.7%). ^{1}H NMR (300 MHz, Acetone-d_6) δ = 1.79 (m, 1H; CH_2), 2.25 (m, 1H; CH_2), 2.54 (m, 1H; CH_2), 2.79 (s, 3H; OCH_3), 3.59 (s, 1H; CH_2), 3.92 (m, 1H; CH_2), 3.96 (m, 2H; C_5H_4), 4.05(m, 5H; Cp), 4.15 (s, 1H; CH_2), 4.22 (m, 2H; C_5H_4), 6.59(d, J = 8.8 Hz, 2H; C_6H_4), 6.74 (t, J = 9.5 Hz, 4H; C_6H_4), 7.54 (d, J = 8.7 Hz, 2H; C_6H_4), 8.22 (s, 1H; OH), 8.28 (s, 1H; OH); ^{13}C NMR (75 MHz, acetone-d_6) δ = 27.3 (CH_2), 37.1 (CH_2), 52.9 (OCH_3), 66.7 (CH; C_5H_4), 66.9 (CH; C_5H_4), 69.2 (5 CH; Cp), 69.9 (CH; C_5H_4), 70.4 (OCH_2), 71.9 (CH; C_5H_4), 91.0 (C), 92.1 (C), 96.9 (C), 113.5 and 114.2 (4 CH; C_6H_4), 130.7 (C; C_6H_4), 131.8 (C; C_6H_4),

133.2 and 133.6 (4 CH; C_6H_4), 156.9 (C; C_6H_4), 157.2 (C); MS-ESI *m/z*: 507 $(M+Na)^+$; HRMS (TOF MS ESI^+, $C_{28}H_{28}FeNaO_4$, $[M]^{\bullet+}$) calcd: 507.1235, found: 507.1218.

Reaction of QM 4b with mercaptoethanol

Freshly made Ag_2O (0.22 g, 0.9 mmol) was added to a solution of 4,4'-(5-hydroxy-2-ferrocenylpent-1-ene-1,1-diyl)diphenol **3b** (0.1 g, 0.23 mmol) in 6 ml of acetone. The dark grey mixture became a dark red suspension about 5 minutes later. The reaction was monitored by TLC until complete conversion of the starting material (20 minutes). Filtration was followed by adding 0.1 ml mercaptoethanol and 60 mg NaOH, the red suspension became orange and clear immediately. The solution was diluted with ethyl acetate and washed twice with water, the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give **15b** (90 mg, yield: 75%). ^1H NMR (300 MHz, Acetone-d_6) δ = 2.15 (m, 2H; CH_2), 2.41 (m, 1H; CH_2), 2.80 (m, 1H; CH_2), 3.20 (m, 2H; CH_2), 3.26 (s, 1H; CH_2), 3.49 (t, *J* = 5.8 Hz, 1H; OH), 3.90 (m, 1H; CH_2), 4.01 (s, 1H; CH_2), 4.06 (s, 6H; Cp and C_5H_4), 4.23 (m, 1H; C_5H_4), 4.32 (m, 2H; C_5H_4), 6.61(dd, *J* = 9.0, 2.7 Hz, 4H; C_6H_4), 7.10 (d, *J* = 8.7 Hz, 2H; C_6H_4), 7.43 (d, *J* = 8.9 Hz, 2H; C_6H_4), 8.20 (s, 1H; OH), 8.27 (s, 1H; OH); ^{13}C NMR (75 MHz, acetone-d_6) δ = 27.7 (CH_2), 35.1 (CH_2), 39.7 (CH_2), 61.6 (CH_2), 61.6 (CH_2), 66.6 (CH; C_5H_4), 66.9 (CH; C_5H_4), 69.4 (5 CH; Cp), 70.2 (CH_2), 70.4 (CH; C_5H_4), 71.4 (CH; C_5H_4), 93.4 (C), 96.8 (C), 113.6 and 113.9 (4 CH; C_6H_4), 133.9 and 134.2 (4 CH; C_6H_4), 135.1 (2 C; C_6H_4), 156.3 and 156.6 (2 C; C_6H_4); MS-ESI *m/z*: 553 $(M+Na)^+$; HRMS (TOF MS ESI^+, $C_{29}H_{30}FeNaO_4S$, $[M]^{\bullet+}$) calcd: 553.1112, found: 553.1107. Anal. Calcd for $C_{29}H_{30}FeO_4S(H_2O)_{2.5}$: C, 60.52; H, 6.13. Found: C, 60.78; H, 6.04.

Reaction of QM 4b with N-Acetyl-L-cysteine methyl ester

Freshly made Ag_2O (0.22 g, 0.9 mmol) was added to a solution of 4,4'-(5-hydroxy-2-ferrocenylpent-1-ene-1,1-diyl)diphenol **3b** (0.1 g, 0.23 mmol) in 6 ml of acetone. The dark grey mixture became a dark red suspension about 5 minutes later. The reaction was monitored by TLC until complete conversion of the starting material (20 minutes). Filtration was followed by adding N-acetyl-L-cysteine methyl ester (0.23 g, 1.3 mmol) and 60 mg NaOH, the red suspension became orange and clear immediately. The

solution was diluted with ethyl acetate and washed twice with water, the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give **16b** (120 mg, yield: 83%). ^{1}H NMR (300 MHz, Acetone-d_6) δ = 1.85 (d, J = 5.2 Hz, 3H; CH_3), 2.26 (m, 1H; CH_2), 2.40 (m, 1H; CH_2), 2.51 (m, 1H; CH_2), 2.80 (m, 1H; CH_2), 3.14 (s, 1H; CH_2), 3.57 (s, 3H; OCH_3), 3.89 (s, 1H; CH_2), 4.02 (m, 1H; CH_2), 4.06 (s, 5H; Cp), 4.16 - 4.45 (m, 4H; C_5H_4), 6.62(d, J = 8.5 Hz, 4H; C_6H_4), 6.90 (m, 1H; NH), 7.05 (t, J = 8.8 Hz, 2H; C_6H_4), 7.39 (t, J = 8.7 Hz, 2H; C_6H_4), 8.25 (s, 1H; OH), 8.33 (s, 1H; OH); ^{13}C NMR (75 MHz, acetone-d_6) δ = 22.6 (CH_3), 27.8 (CH_2), 34.0 (CH_2), 39.9 (CH_2), 52.5 (CH_3), 52.7 (CH), 52.9 (OCH_3), 66.7 (CH; C_5H_4), 67.0 (CH; C_5H_4), 69.5 (5 CH; Cp), 70.0 (CH_2), 70.3 (CH; C_5H_4), 71.2 (CH; C_5H_4), 71.7 (C), 74.5 (C), 93.5 (C), 113.2 and 113.7 (4 CH; C_6H_4), 133.9 and 134.0 (4 CH; C_6H_4), 134.7 (2 C; C_6H_4), 156.4 and 156.8 (2 C; C_6H_4), 171.9 (C=O), 178.1 (C=O); MS-ESI *m/z*: 652 $(M+Na)^+$. HRMS (TOF MS ESI$^+$, $C_{33}H_{35}FeNNaO_6S$, $[M]^{\bullet+}$) calcd: 652.1432, found: 652.1427.

Reaction of QM 4a under acid conditions

With 1N HCl. Freshly made Ag_2O (0.5 g, 2 mmol) was added to a solution of **3a** (0.19 g, 0.43 mmol) in 10 ml of acetone. The dark grey mixture became a dark red suspension about 5 minutes later. The reaction was monitored by TLC until complete conversion of the starting material (20 minutes). Filtration was followed by adding 5 drops of 1N HCl, the red suspension became orange and clear immediately. The solution was diluted with ethyl acetate and washed twice with water, the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give 4 compounds. **4-((R)-hydroxy(phenyl)((R)-2-ferrocenyltetrahydrofuran-2-yl)methyl)phenol (9a)** as a brown solid 50 mg, yield: 26%. ^{1}H NMR (300 MHz, Acetone-d_6) δ = 1.74 (m, 1H; CH_2), 2.62 (m, 2H; CH_2), 3.56 (s, 1H; OH), 3.76 (m, 1H; CH_2), 3.97 (m, 2H; C_5H_4), 4.05 (m, 2H; CH_2), 4.14 (m, 2H; C_5H_4), 4.20(s, 5H; Cp), 4.24 (m, 1H; CH_2), 6.71(m, 2H; C_6H_4), 7.25 (m, 3H; C_6H_5), 7.55 (m, 2H; C_6H_4), 7.72 (m, 2H; C_6H_5), 8.08 and 8.19 (s, 1H; OH). ^{13}C NMR (75 MHz, acetone-d_6) δ = 26.8 (CH_2), 38.3 (CH_2), 67.2 (CH; C_5H_4), 67.8 (CH; C_5H_4), 68.2 (CH; C_5H_4), 69.5 (5 CH; Cp), 70.4 (CH; C_5H_4), 70.5 (OCH_2), 80.8 (C), 91.9 (C), 96.8 (C), 114.5 and 114.8 (2 CH; C_6H_4), 126.8 (CH; C_6H_5), 127.7 (CH; C_6H_5), 128.0 (2

CH; C_6H_4), 129.9 (2 CH; C_6H_5), 132.1 (CH; C_6H_5), 138.7 (C; C_6H_4), 145.8 (C; C_6H_5), 156.5 and 156.7 (C); MS-CI (NH_3) *m/z*: 455$(M+H)^+$. HRMS calcd for $C_{27}H_{26}FeO_3$ $(M)^+$: 454.1231, found: 454.1225. Anal. Calcd for $C_{27}H_{26}FeO_3(H_2O)_{0.7}$: C, 69.45; H, 5.91. Found: C, 69.68; H, 6.28. **5-hydroxy-1-(4-hydroxyphenyl)-1-phenyl-1-ferrocenylpentan-2-one (6a)** as a brown solid 45 mg, yield: 24%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.39 (s, 1H, OH), 7.39 – 7.19 (m, 3H, C_6H_5), 7.10 (dd, *J* = 7.9, 1.7 Hz, 2H, C_6H_4), 6.93 (d, *J* = 8.8 Hz, 2H, C_6H_4), 6.78 (d, *J* = 8.8 Hz, 2H, C_6H_5), 4.29(s, 2H, C_5H_4), 4.18(s, 5H, C_5H_5), 3.93 (s, 1H, C_5H_4), 3.80 (s, 1H, C_5H_4), 3.55 (m, 3H, OH and OCH_2), 2.90 (m, 2H, CH_2), 1.82 (m, 2H, CH_2); ^{13}C NMR (75 MHz, Acetone-d_6) δ 208.2 (C=O), 157.1 (C, C_6H_4), 145.2 (C, C_6H_5), 135.4 (C, C_6H_4), 131.8 (2 CH, C_6H_4), 130.8 (2 CH, C_6H_4), 128.1 (2 CH, C_6H_5), 127.5 (CH, C_6H_5), 115.1 (2 CH, C_6H_4), 90.5 (C, C_5H_4), 71.8 (2 CH, C_5H_4), 70.4 (5 CH, C_5H_5), 69.0 (2 CH, C_5H_4), 67.0 (C), 61.8 (OCH_2), 38.9 (CH_2), 28.8 (CH_2); MS-EI *m/z*: 454 $(M)^+$. HRMS calcd for $C_{27}H_{26}FeO_3$ $(M)^+$: 454.1231, found: 454.1229. Anal. Calcd for $C_{27}H_{26}FeO_3(H_2O)_{0.5}$: C, 69.99; H, 5.87. Found: C, 70.18; H, 6.14. **4-hydroxy-1-ferrocenylbutan-1-one (7)** as a brown solid 10 mg, yield: 9%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 4.82– 4.78 (m, 2H, C_5H_4), 4.54 – 4.50 (m, 2H, C_5H_4), 4.22 (s, 5H, C_5H_5), 3.62 (m, 2H, OH and OCH_2), 2.86 (m, 2H, CH_2), 1.93– 1.81 (m, 2H, CH_2); ^{13}C NMR (75 MHz, Acetone-d_6) δ 203.75 (C=O), 80.56 (C, C_5H_4), 72.68 (2 CH, C_5H_4), 70.46 (5 CH, C_5H_5), 69.97 (2 CH, C_5H_4), 61.94 (OCH_2), 36.49 (CH_2), 28.18 (CH_2). **(4-hydroxyphenyl)(phenyl)methanone (8a)** as a brown solid 9 mg, yield: 11%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.26 (s, 1H, OH), 7.82– 7.68 (m, 4H, C_6H_4), 7.67– 7.68 (m,1H, C_6H_5), 7.58 – 7.47 (m, 2H, C_6H_5), 6.97 (d, *J* = 8.8 Hz, 2H, C_6H_5); ^{13}C NMR (75 MHz, Acetone-d_6) δ 195.2 (C=O), 162.5 (C, C_6H_4), 139.5 (C, C_6H_5), 133.4 (2 CH, C_6H_4), 132.5 (CH, C_6H_5), 130.2 (2 C, C_6H_4), 129.1 (2 CH, C_6H_5), 116.0 (2 CH, C_6H_5).

Reaction of QM 4a with mercaptoethanol

Freshly made Ag_2O (0.4 g, 2 mmol) was added to a solution of **3a** (0.29 g, 0.66 mmol) in 6 ml of acetone. The dark grey mixture became a dark red suspension about 5 minutes later. The reaction was monitored by TLC until complete conversion of the starting material (20 minutes). Filtration was followed by adding 0.1 ml mercaptoethanol and 60 mg NaOH, the red suspension became orange and clear immediately. The solution was diluted with ethyl acetate and washed twice with water, the organic

layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (1:2) to give **15a** (100 mg, yield: 65%). ^{1}H NMR (300 MHz, Acetone-d_6) δ = 2.15 (m, 2H; CH_2), 2.44 (m, 1H; CH_2), 2.85 (m, 1H; CH_2), 3.19 (t, *J* = 6.8 Hz, 2H; CH_2), 3.23 (s, 1H; CH_2), 3.48 (brs, 1H; OH), 3.90 (m, 1H; CH_2), 4.02 (s, 1H; CH_2), 4.07 (s, 5H; Cp), 4.23 (m, 2H; C_5H_4), 4.36 (m, 2H; C_5H_4), 6.63 (dd, *J* = 8.9, 3.2 Hz, 2H; C_6H_4), 7.10 (m, 4H; C_6H_4), 7.31 (d, *J* = 5.8 Hz, 1H; C_6H_5), 7.42 (d, *J* = 8.8 Hz, 1H; C_6H_5), 7.61 (m, 1H; C_6H_5), 8.20 and 8.27 (s, 1H; OH); ^{13}C NMR (75 MHz, acetone-d_6) δ = 27.7 (CH_2), 35.2 (CH_2), 39.8 (CH_2), 61.6 (CH_2), 66.7 (CH; C_5H_4), 67.0 (CH; C_5H_4), 69.5 (5 CH; Cp), 70.3 (CH_2), 70.5 (CH; C_5H_4), 71.4 (CH; C_5H_4), 93.4 (C), 96.6 (C), 113.7 and 114.0 (2 CH; C_6H_4), 126.7 (CH; C_6H_5), 126.9 (CH; C_6H_5), 127.1 (CH; C_6H_5), 132.8 and 133.0 (2 CH; C_6H_4),133.8 and 134.0 (2 CH; C_6H_5), 134.2 (C), 143,7 abd 144.6 (C), 156.4 and 156.8 (C); MS-EI *m/z*: 514 M^+. HRMS (TOF MS ESI$^+$, $C_{29}H_{30}FeNaO_3S$, $[M]^{\bullet+}$) calcd: 537.1163, found: 537.1158. Anal. Calcd for $C_{29}H_{30}FeO_3S(H_2O)_{1.5}$: C, 64.33; H, 6.14. Found: C, 64.38; H, 5.98.

Reaction of QM 4a with N-Acetyl-L-cysteine methyl ester

Freshly made Ag_2O (0.4 g, 2 mmol) was added to a solution of **3a** (0.29 g, 0.66 mmol) in 6 ml of acetone. The dark grey mixture became a dark red suspension about 5 minutes later. The reaction was monitored by TLC until complete conversion of the starting material (20 minutes). Filtration was followed by adding N-Acetyl-L-cysteine methyl ester (0.27 g, 1.5 mmol) and 60 mg NaOH, the red suspension became orange and clear immediately. The solution was diluted with ethyl acetate and washed twice with water, the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with PE:EtOAc (2:1) to give **16a** (120 mg, yield: 65%). ^{1}H NMR (300 MHz, Acetone-d_6) δ = 1.85 (d, *J* = 5.3 Hz, 3H; CH_3), 2.23 (m, 2H; CH_2), 2.47 (m, 2H; CH_2), 2.80 (m, 1H; CH_2), 3.14 (s, 1H; CH_2), 3.57 (s, 3H; OCH_3), 3.89 (s, 1H; CH_2), 4.03 (m, 1H; CH_2), 4.07 (s, 5H; Cp), 4.25 (m, 2H; C_5H_4), 4.36 (m, 2H; C_5H_4), 6.64(m, 2H; C_6H_4), 7.01 (m, 2H; C_6H_4), 7.01 (m, 3H; C_6H_5), 7.26 (m, 1H; NH), 7.38 (d, *J* = 8.7 Hz, 1H; C_6H_5), 7.57 (d, *J* = 5.8 Hz, 1H; C_6H_5), 8.29 and 8.32 (s, 1H; OH); ^{13}C NMR (75 MHz, acetone-d_6) δ = 22.6 (CH_3), 27.7 (CH_2), 34.0 (CH_2), 40.0 (CH_2), 52.6 (OCH_3), 52.8 (CH), 66.8 (CH; C_5H_4), 67.2 (CH; C_5H_4), 69.6 (5 CH; Cp), 70.1 (CH_2), 70.4 (CH; C_5H_4), 71.2 (CH; C_5H_4), 93.4 (C), 96.3 (C), 113.9 and 114.2 (2 CH;

C_6H_4), 127.0 and 127.3 (2 CH; C_6H_4), 132.8 (CH; C_6H_5), 134.0 (4 C; C_6H_5), 134.3 (C), 144.3 (C), 156.6 and 157.0 (C), 169.8 and 170.9 (C=O), 171.8 (C=O); MS-ESI *m/z*: 614 M^+, 636 $(M+Na)^+$. HRMS (TOF MS ESI$^+$, $C_{33}H_{35}FeNNaO_5S$, $[M]^{\bullet+}$) calcd: 636.1483, found: 636.1478. Anal. Calcd for $C_{33}H_{35}FeNO_5S(H_2O)_{2.5}$: C, 60.18; H, 6.12; N, 2.13. Found: C, 60.25; H, 5.91; N, 2.06.

X-Ray crystal structure determination of 10b

A suitable crystal of compound **10b** was mounted and transferred into a cold nitrogen gas stream. Intensity data was collected with a Bruker Kappa-APEX2 system using micro-source Cu-Kα radiation. Data collection was carried out with the Bruker APEX2 suite of programs. Unit-cell parameters determination, integration and data reduction were performed with SAINT. SADABS was used for scaling and multi-scan absorption corrections. The structure was solved with SHELXT-2014[3] and refined by full-matrix least-squares methods with SHELXL-2014[3] using the WinGX suite[4]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions and refined with a riding model. The structure was deposited at the Cambridge Crystallographic Data Centre with number CCDC 1527404 and can be obtained free of charge via www.ccdc.cam.ac.uk.

Kinetic experiments of QM 4b. The disappearance of **4b** (0.15 mM) in 50 mM phosphate buffer (1 mL, pH 7.4, 37 °C) was followed by monitoring the decrease in UV absorbance at 325 nm (1 min/scan) using a Cary 50 Scan UV/VIS spectrophotometer. The disappearance of **4b** (0.15 mM) in the presence of thiols nucleophiles (50 mM) in 50 mM phosphate buffer (1 mL, pH 7.4, 37 °C) was followed by monitoring the decrease in absorbance at 325 nm (5 s/scan) at 37 °C. Pseudo first rate constants were determined in triplicate for at least four half-lives.

Peroxidase oxidation of 3a and 3b.

3a and **3b** at 0.1 ~ 0.25 mM final concentration, were incubated in 50mM phosphate buffer (pH 7.4, 37 °C). When indicated, 0.02% ~ 0.1% H_2O_2 and 1 ~ 4 equivalents HRP were also added after 5 min preincubation. The oxidation was followed by UV-Vis, HPLC and LC-MS.

Incubation of 3a and 3b with liver microsomes in the absence or presence of thiols.

Rat liver microsomes were isolated from rat pretreated for 7 days by 1g/L phenobarbital in drinking water (2 nmole P450/mg protein); [5] All the experiments with animals were performed in accordance with the French Agricultural and Fishing Ministry regulations, following an agreement from the French Ministry of Education and Research (Nb APAFIS#794-2016102716338280 v2). Male Sragues Dawley rats (220-250 g) were used for the study. Human liver microsomes were obtained from Corning as UltraPool HLM-150 containing 350 pmol P450/mg protein. Typical incubations were performed in potassium phosphate buffer (0.1 M, pH 7.4) containing microsomes (0.5-1 mg protein/mL for rat microsomes and 1 mg/mL for HLM), 1 mM NADP, 15 mM glucose-6-phosphate, 2 unit/mL of glucose-6-phosphate dehydrogenase, and substrate (5-500 μM) at 37 °C. Reactions were stopped either by adding one-half volume of CH_3CN:CH_3COOH (9:1) and centrifugation of precipitated proteins (12000 g, 10 min) or by solid-phase extraction using Oasis columns (Waters, St. Quentin en Yvelines, France) (1 mL loading, 1 mL water wash, and 1 mL CH_3OH elution), evaporation of the solvent with N_2, and redissolution in HPLC mobile phase.

HPLC-MS analyses.

HPLC-MS studies were performed on a Surveyor HPLC instrument coupled to a LCQ Advantage ion trap mass spectrometer (Thermo, Les Ulis, France), using a Biobasic C18 column (100 mm x 2 mm, 3 μm) and a 20 min linear gradient of A) ammonium acetate (10 mM, pH 4.6) to B) CH_3CN:CH_3OH:H_2O (7:2:1) mixture at 200 μL/min. For some compounds an alternative gradient system was used: A) H_2O: HCOOH 0.5% and B) CH_3CN: HCOOH 0.1%. Mass spectra were obtained by electrospray ionization (ESI) in positive ionization mode detection under the following conditions: source parameters: sheath gas, 20; auxiliary gas, 5; spray voltage, 4.5 kV; capillary temperature, 200 °C; capillary voltage, 15 V; and m/z range for MS recorded generally between 200 and 900. Semiquantitative analysis of the yield of different metabolites from the two quinone methide pathways was achieved by comparing the areas under the respective peaks of different compounds visible in the UV traces of the LC-MS analysis. High resolution HPLC-MS was performed with a Shimadzu Prominence HPLC system coupled to an Exactive-Orbitrap mass spectrometer (Thermo, Les Ulis, France), using a Satisfaction C18 column 100

mm x 2 mm, 3 μm) (CIL, Sainte Foix la Grande, France) and the above alternative gradient and the same source parameters.

Cell Culture and Proliferation Assay.

Stock solutions (10 mM) of the compounds to be tested were prepared in DMSO and were kept at -20 °C in the dark. Serial dilutions in Dulbecco's modified eagle medium (DMEM) without phenol red/Glutamax I were prepared just prior to use. DMEM without phenol red, Glutamax I and fetal bovine serum were purchased from Gibco; MDA-MB-231 cells were obtained from ATCC (Manassas, VA, USA). Cells were maintained in a monolayer culture in DMEM with phenol red/Glutamax I supplemented with 9% fetal bovine serum at 37 °C in a 5% CO_2/air-humidified incubator. For proliferation assays, MDA-MB-231 cells were plated in 1 mL of DMEM without phenol red, supplemented with 9% decomplemented and hormone-depleted fetal bovine serum, 1% kanamycin, 1% Glutamax I and incubated. The following day (D0), 1 mL of the same medium containing the compounds to be tested was added to the plates. After 3 days (D3) the incubation medium was removed and 2 mL of the fresh medium containing the compounds was added. At different days (D4, D5), the protein content of each well was quantified by methylene blue staining as follows: cell monolayers were fixed for 1 h at room temperature with methylene blue (1mg mL-1 in 50:50 water/MeOH mixture), then washed with water. After addition of HCl (0.1 M, 2 mL), the plate was incubated for 1 h at 37 °C and then the absorbance of each well (4 wells for each concentration) was measured at 655 nm with a Biorad spectrophotometer. The results are expressed as the percentage of proteins versus the control. Two independent experiments, run in quadruplicate, were performed.

A2780 and A2780cisR ovarian carcinoma cells were grown in RPMI 1640 supplemented with 10% fetal calf serum (FCS) and 1% glutamine. MRC-5 cells were grown in Gibco medium DMEM supplemented with 10% fetal calf serum (FCS) and 1% glutamine. Cells were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell growth inhibition was determined by an MTS assay according to the manufacturer's instructions (Promega, Madison, WI, USA). Briefly, the cells were seeded in 96-well plates (2.5×10^3 cells/well) containing 100 μL of growth medium. After 24 h of culture, the cells were treated with the tested compounds at 10 different final concentrations. After 72 h of incubation, 20 μL of

CellTiter 96® AQ_{ueous} One Solution Reagent was added for 2 h before recording absorbance at 490 nm with a spectrophotometric plate reader PolarStar Omega (BMG Labtech, USA). The dose-response curves were plotted with Graph Prism software and the IC_{50} values were calculated using the Graph Prism software from polynomial curves (four or five-parameter logistic equations).

NCI/DTP cytotoxicity tests.

The protocol for the determination of cytotoxicity on the 60 cell line panel can be found at http://dtp.nci.nih.gov/branches/btb/ivclsp.html; The DTP homepage can be accessed at http://dtp.cancer.gov/.

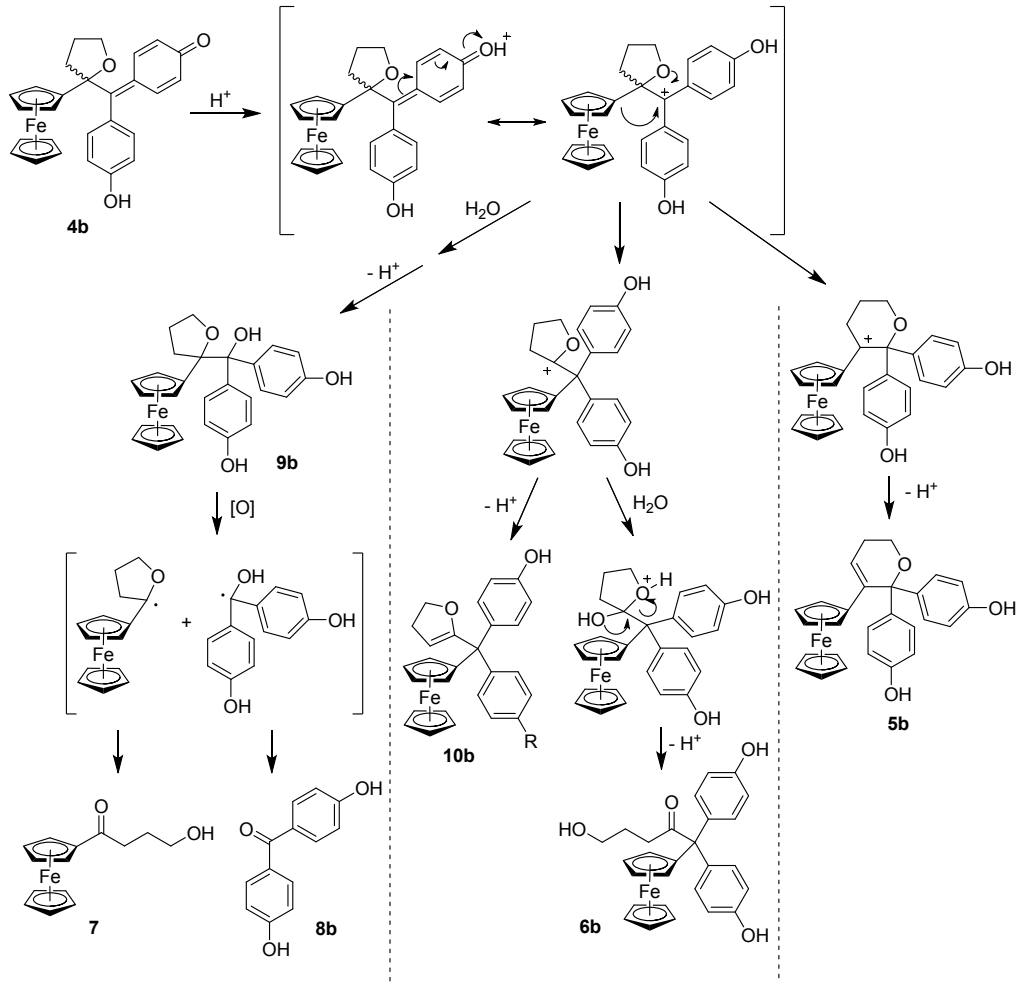

Figure S1. Proposed mechanisms for the formation of products **5 - 10**.

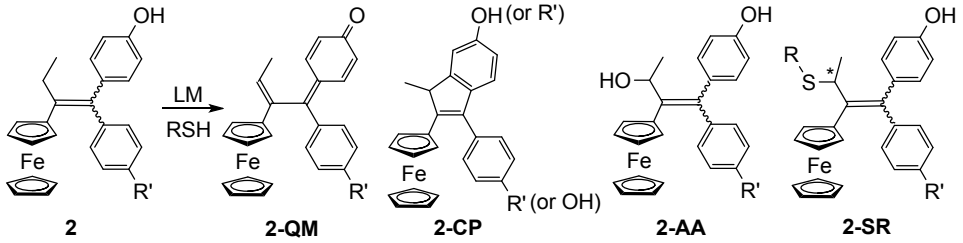

Figure S2. Products obtained from incubation of **2** with liver microsomes (LM) and NADPH; R` = OH, or $O(CH_2)_3NMe_2$.

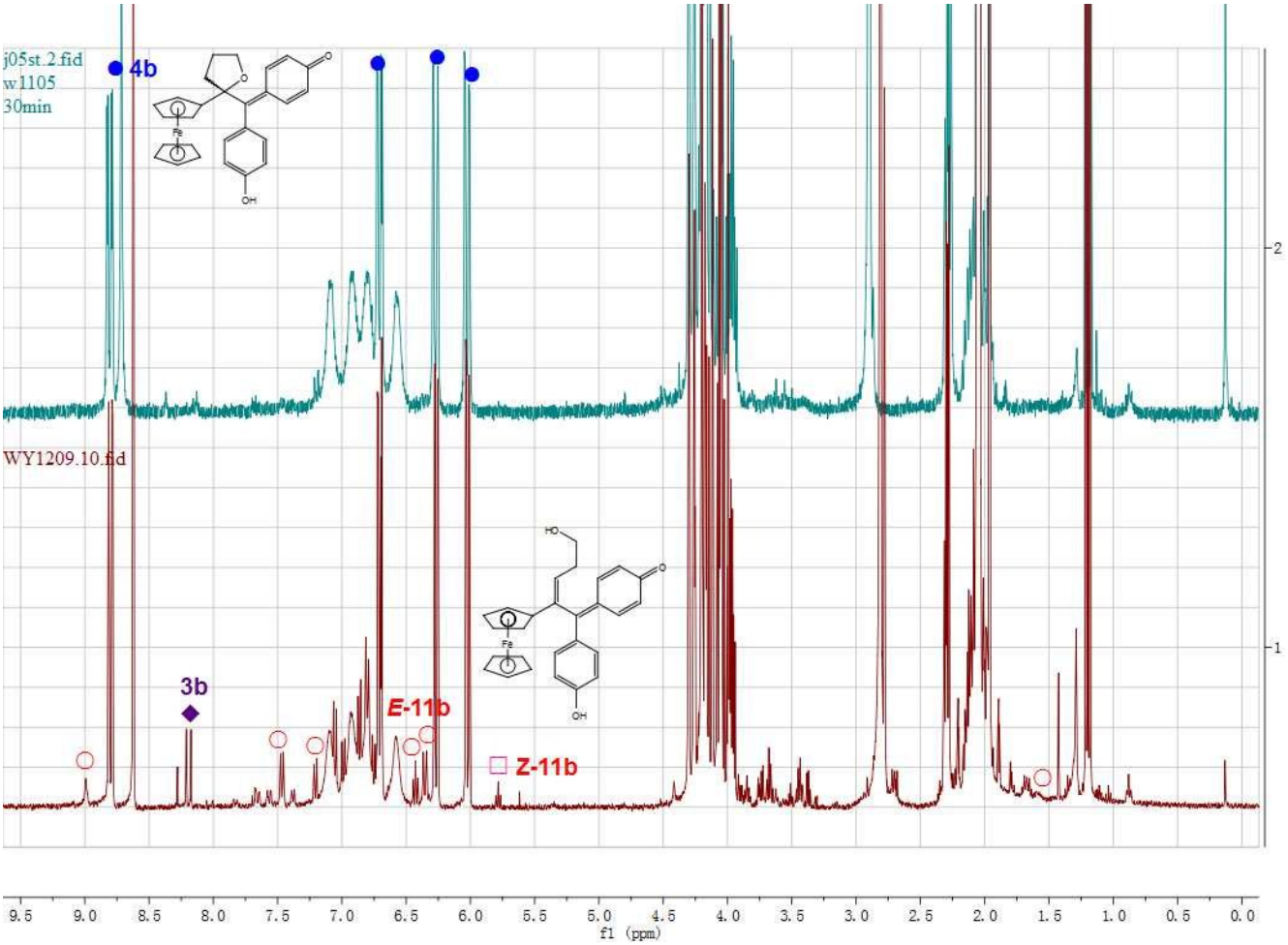

Figure S3. The characteristic assignment of QM **4b** (**blue** solid point**)**, QM ***E*-11b** (**brown** hollow point**)** and QM ***Z*-11b** (**brown** hollow grid**)** (^{1}H NMR spectrum of **3b** after 30 min oxidation by Ag_2O in acetone-d_6, upper, 100 mM substrate with 5 equivalents of Ag_2O; lower, 5 mM substrate with 1 equivalent of Ag_2O).

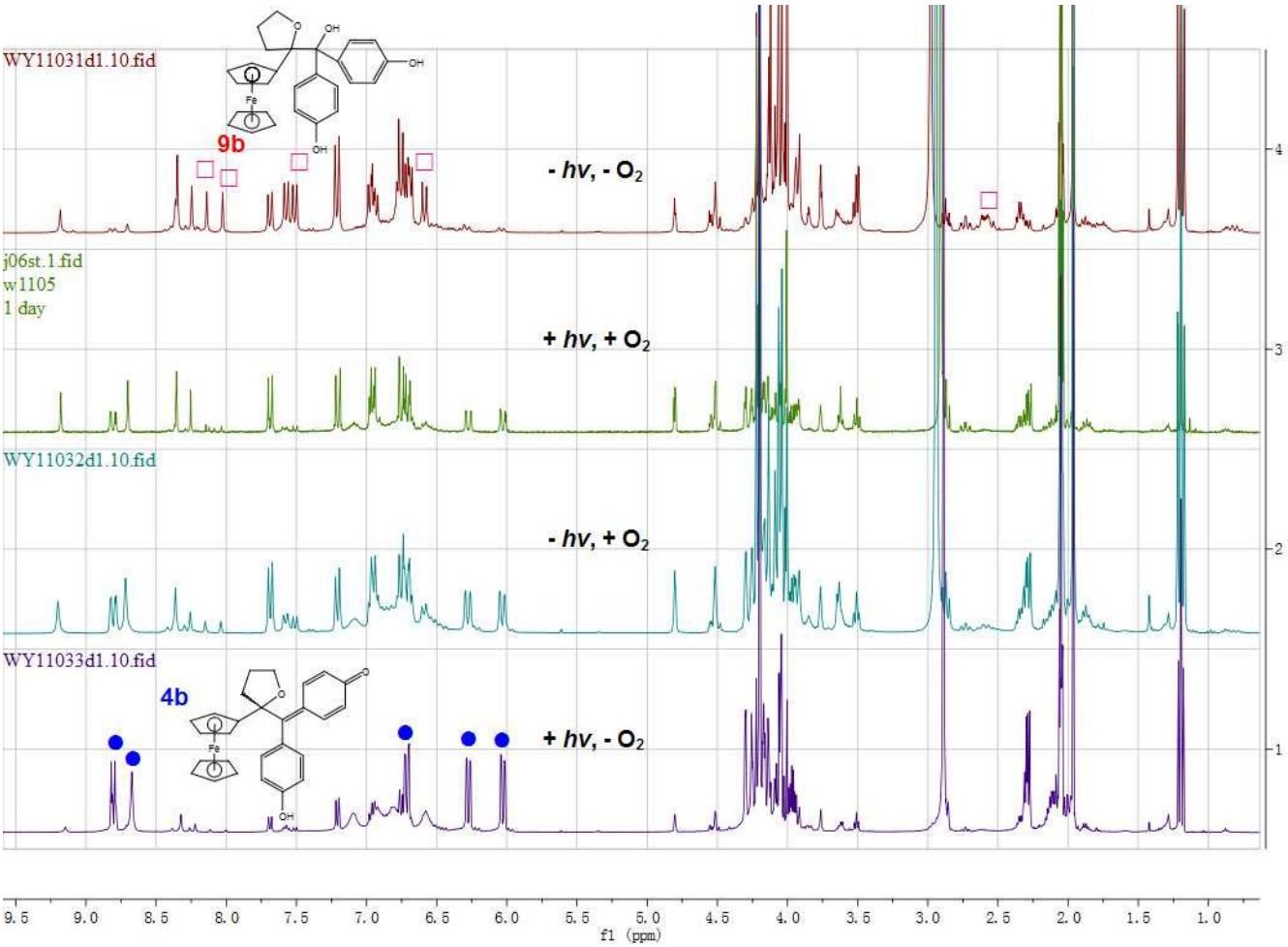

Figure S4. ^{1}H NMR study of the evolution of **4b** (**blue** solid point**)** in acetone-d_6 in 24 hrs under dark and anaerobic conditions (- *hv*, - O_2), light and aerobic conditions (+ *hv*, + O_2), dark and aerobic conditions (- *hv*, + O_2), light and anaerobic conditions (- *hv*, + O_2). Only very small amount of compound **9b** (**brown** hollow grid**)** was observed under light or aerobic conditions.

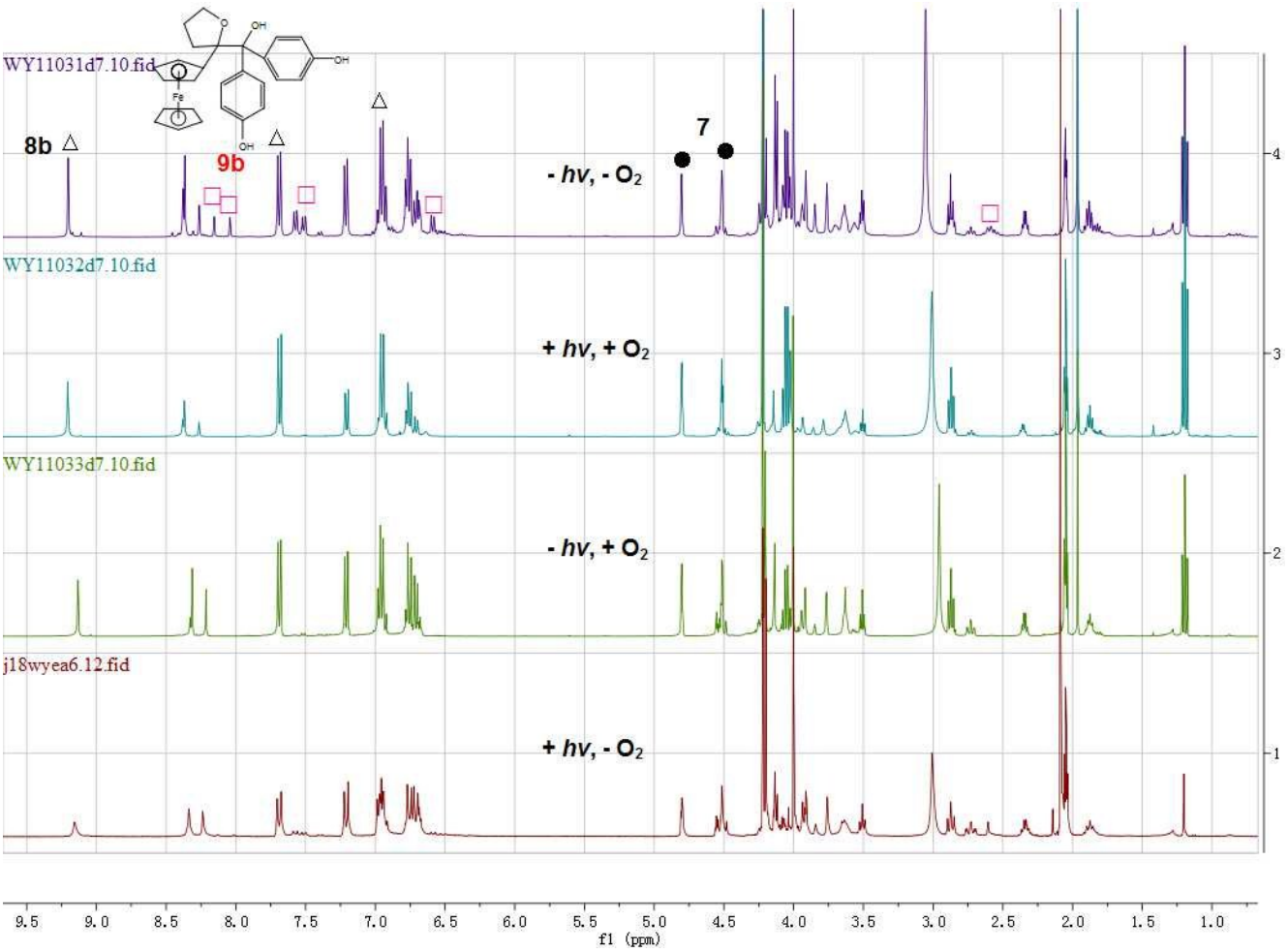

Figure S5. ^{1}H NMR study of the evolution of **4b** in acetone-d_6 in 7 days under dark and anaerobic conditions (- *hv*, - O_2), light and aerobic conditions (+ *hv*, + O_2), dark and aerobic conditions (- *hv*, + O_2), light and anaerobic conditions (- *hv*, + O_2). Only under dark and anaerobic conditions small amount of compound **9b** (**brown** hollow grid**)** could be observed after 7 days. There are more ketone compounds **7** (**black** solid point**)** and **8b** (**black** hollow triangle**)** in this case compared with those of **4b** in 24 h under identical conditions.

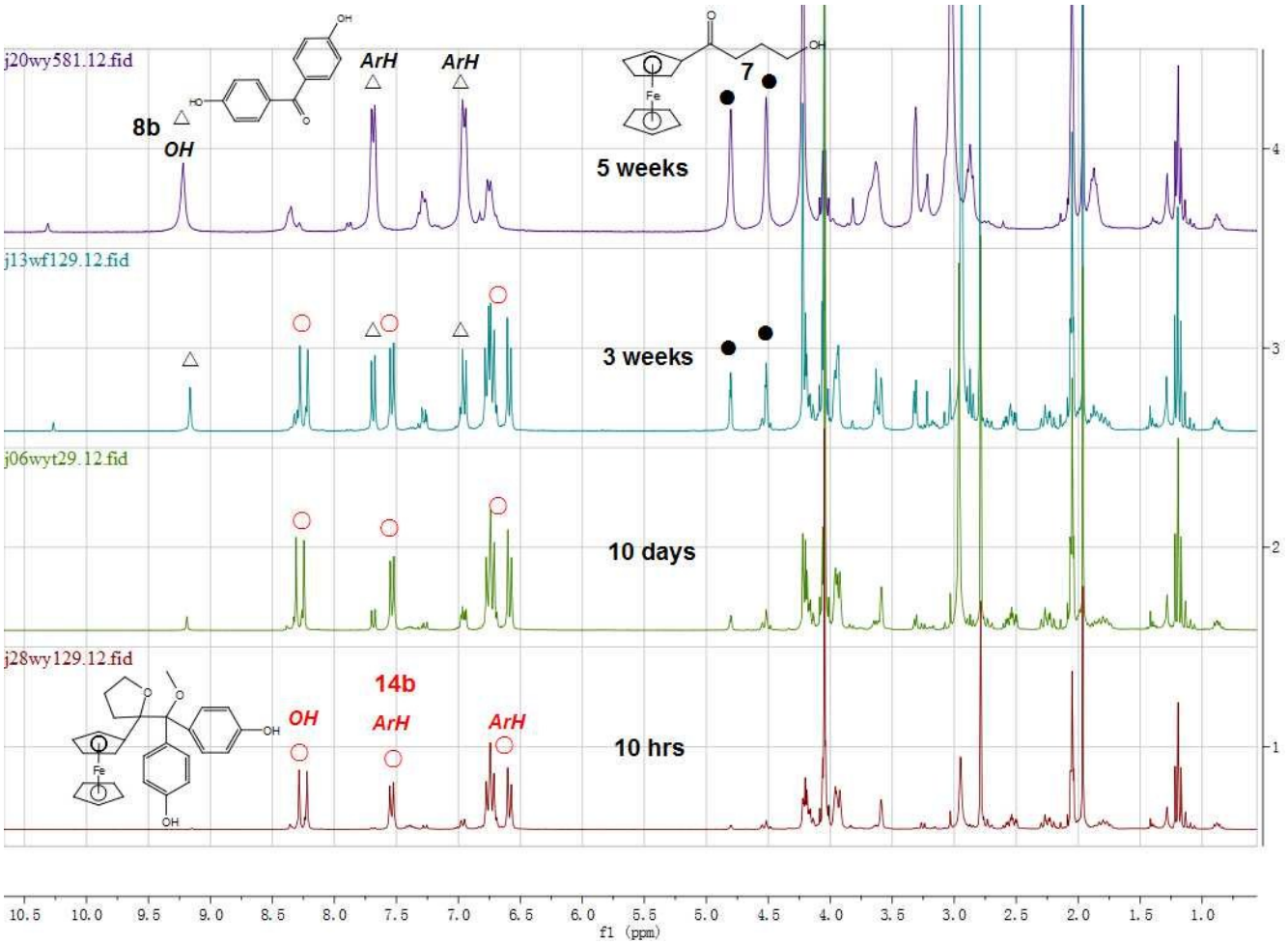

Figure S6. ^{1}H NMR study of the stability of **14b** (**brown** hollow point**)** in acetone-d_6. There are more ketone compounds **7** (**black** solid point**)** and **8b** (**black** hollow triangle**)** after around 5 weeks.

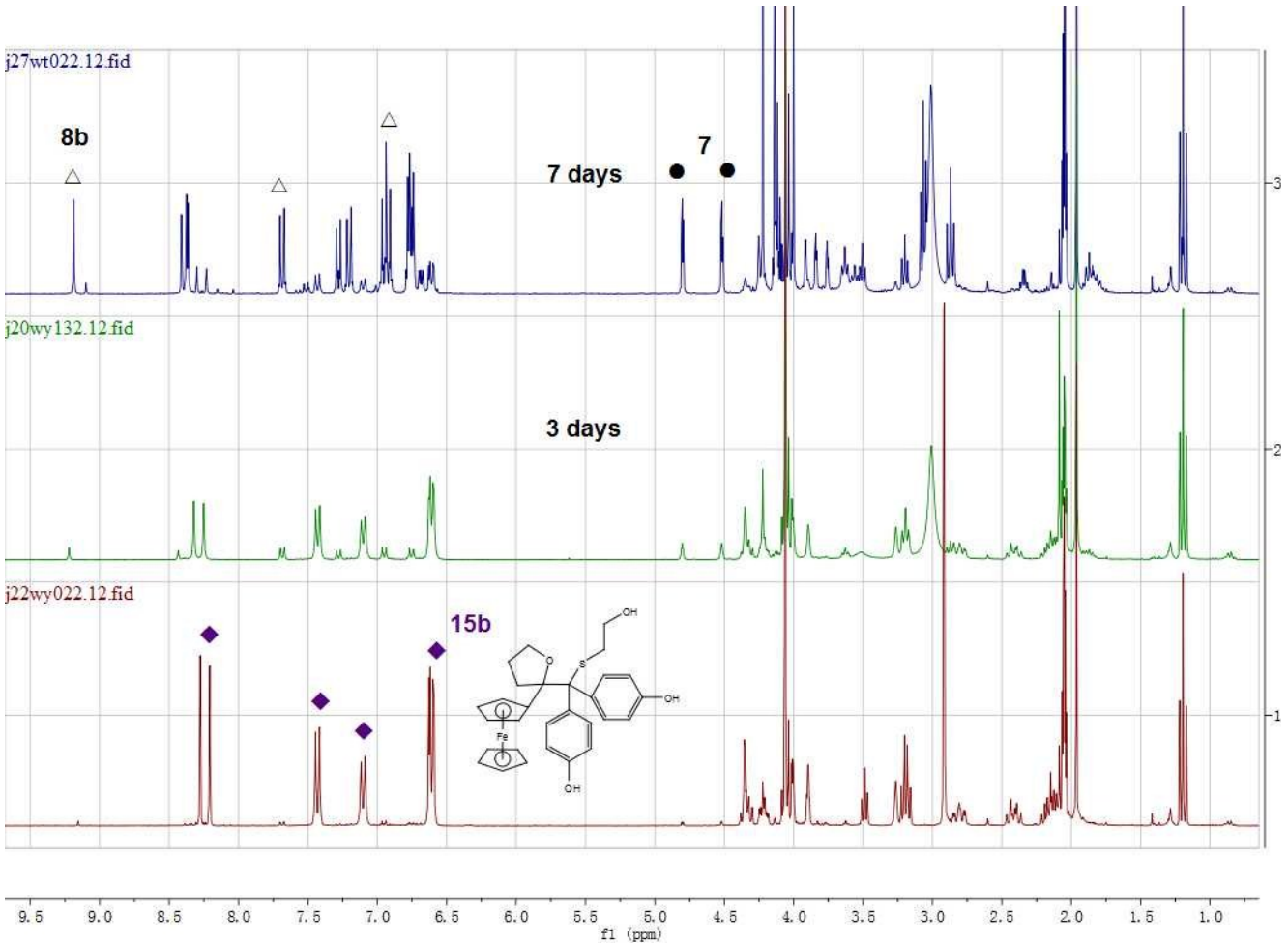

Figure S7. ^{1}H NMR study of the stability of **15b** (**violet** solid diamond**)** in acetone-d_6. There are more ketone compounds **7** (**black** solid point**)** and **8b** (**black** hollow triangle**)** after around one week.

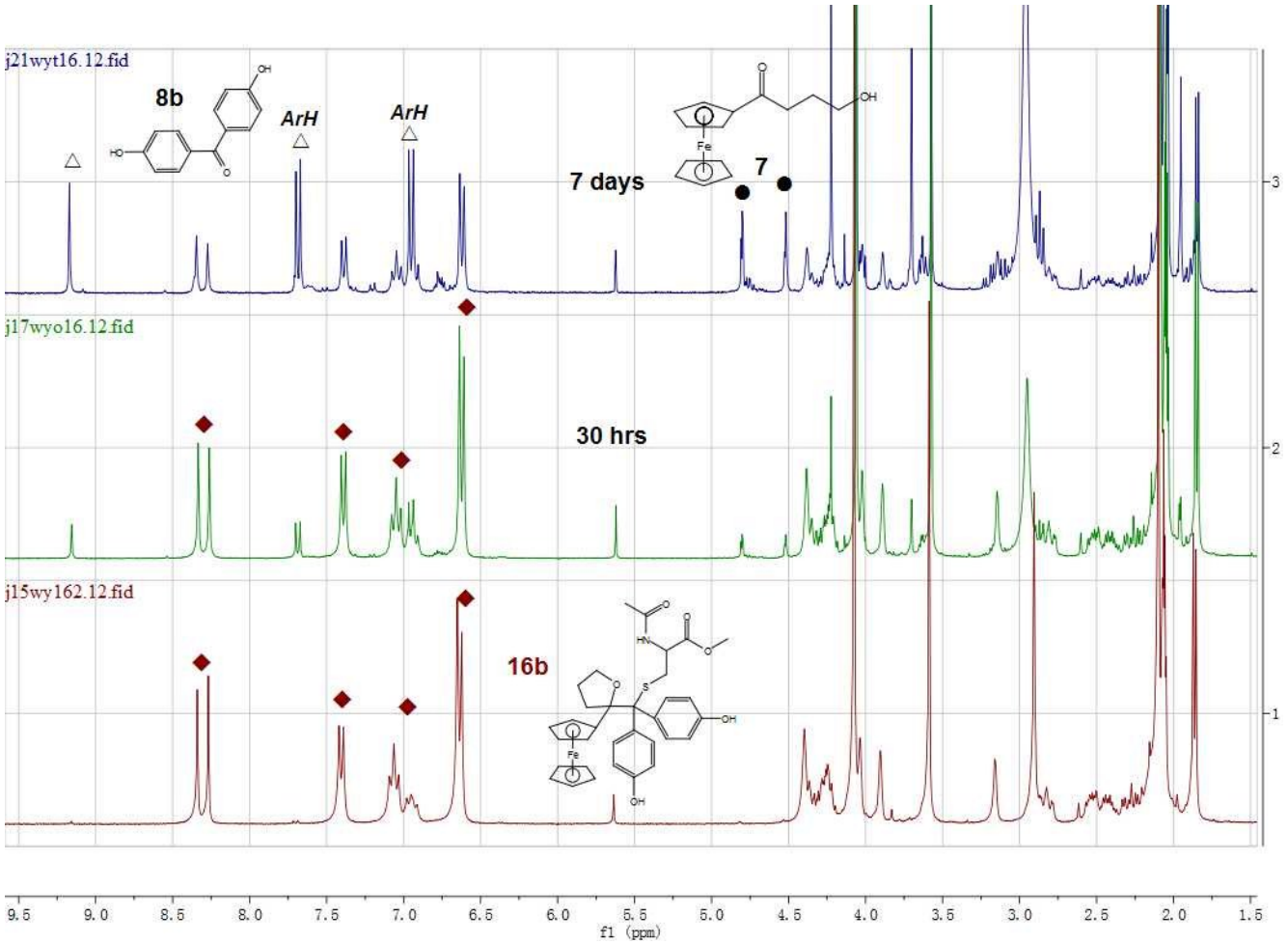

Figure S8. ^{1}H NMR study of the stability of stability of **16b** (**brown** solid diamond**)** in acetone-d_6. There are more ketone compounds **7** (**black** solid point**)** and **8b** (**black** hollow triangle**)** after around one week.

Table S1. Crystallographic Data for **10b**.

10b			
Formula	$C_{27}H_{24}FeO_3$	Selected bond lengths (Å)	
Molecular Weight	452.31	C(1)-C(2)	1.524(3)
Crystal description	Orange stick	C(1)-C(6)	1.530(3)
Crystal size (mm)	0.35x 0.15x 0.02	C(1)-C(16)	1.538(3)
λ (Å)	1.5418	C(1)-C(22)	1.550(3)
Temperature (K)	200(1)	C(2)-C(3)	1.321(3)
Crystal system	Monoclinic	C(2)-O(1)	1.373(3)
Space group	P 2_1/c	C(5)-O(1)	1.449(3)
a (Å)	11.0994(4)	Fe(1)-C(6)	2.051(3)
b (Å)	8.5265(3)	Selected Bond Angles (°)	
c (Å)	21.7146(8)	C(2)-C(1)-C(22)	108.2(2)
α (°)	90	C(2)-C(1)-C(6)	111.9(2)
β (°)	97.392 (3)	C(2)-O(1)-C(5)	106.8(2)
γ (°)	90	C(3)-C(2)-O(1)	113.8(2)
Volume (Å3)	2037.97(13)	C(16)-C(1)-C(6)	109.2(2)
Z	4	C(1)-C(6)-C(7)	125.8(2)
R	0.045	C(2)-C(3)-C(4)	109.3(2)
Rw	0.1217		
GOF	1.068		

Table S2. Diversity of products resulting from oxidation of ferrocenyl compounds **3** by liver microsomes (0.5 mg protein/ ml incubate) in the presence of NADPH, or by the HRP + H_2O_2 system (0.02% HRP + 1 equivalent of H_2O_2).

Comp.	Conditions	QMs 4 pathway							QMs 11 pathway		
		5	**6**	**7**	**8**	**9**	**10**	**Thiol adducts**	**12**	**18**	**Thiol adducts**
3b	PB, HRP + H_2O_2, 3 min	+	trace	+	+	++	trace		+	+	
	PB, LM, 30 min	++	trace	++	++++	trace	trace		trace	++	
	PB, LM, ME, 30 min	++	trace	++	++++	trace	trace	+	trace	+	+
	PB, LM, NACM, 30 min	++	trace	++	++++	trace	trace	++	trace	+	+
	PB, LM, GSH, 30 min	+	trace	++	++	trace	trace	++++	trace	+	+
3a	PB, HRP + H_2O_2, 3 min	+	trace	+	+	++	trace		+	+	
	PB, LM, 30 min	++	trace	++	++++	trace	trace		trace	++	
	PB, LM, ME, 30 min	++	trace	++	++++	trace	trace	+	trace	+	+
	PB, LM, NACM, 30 min	++	trace	++	++++	trace	trace	++	trace	+	+
	PB, LM, GSH, 30 min	+	trace	++	++	trace	trace	++++	trace	+	+

(a) Semiquantitative analysis method was used to determine the amount of products according to their HPLC or LC-MS spectra: trace, < 1%; +, 1% ~ 5%; ++, 5% ~ 30%; ++++, >30%.

Table S3. Diversity of products resulting from the oxidation of ferrocenyl compounds **3** by liver microsomes (0.85 mg protein/ ml incubate) in the presence of NADPH, or by the HRP + H_2O_2 system (0.1% HRP + 4 equivalents of H_2O_2).

Comp.	Conditions	QMs 4 pathway							QMs 11 pathway		
		5	**6**	**7**	**8**	**9**	**10**	**Thiol adducts**	**12**	**18**	**Thiol adducts**
3b	PB, HRP + H_2O_2, 3 min	+	trace	++	++++	+	+		trace	trace	
	PB, LM, 30 min	++	trace	++++	++++	trace	trace		trace	+	
	PB, LM, ME, 30 min	++	trace	++++	++++	trace	trace	trace	trace	+	+
	PB, LM, NACM, 30 min	++	trace	++++	++++	trace	trace	trace	trace	+	+
	PB, LM, GSH, 30 min	+	trace	++++	++++	trace	trace	+	trace	+	trace
3a	PB, HRP + H_2O_2, 3 min	+	trace	++	++++	+	+		trace	trace	
	PB, LM, 30 min	+	trace	++++	++++	trace	trace		trace	+	
	PB, LM, ME, 30 min	++	trace	++++	++++	trace	trace	trace	trace	+	++
	PB, LM, NACM, 30 min	++	trace	++++	++++	trace	trace	trace	trace	+	+
	PB, LM, GSH, 30 min	+	trace	++++	++++	trace	trace	++	trace	+	trace

(a) Semiquantitative analysis method was used to determine the amount of products according to their HPLC or LC-MS spectra: trace, < 1%; +, 1% ~ 5%; ++, 5% ~ 30%; ++++, >30%.

Table S4. Retention times (RT), MS, and MS^2 properties of thiol adducts **15**, **16**, **17** resulting from QM **4**, and **19**, **20**, **21** resulting from QM **11**.

Compound	*M*r (Calc.)	*m/z*		RT
		MS	MS^2	
15a(1,6-ME)	514	537 $[M + Na]^+$	437, 371, 255	16.67
16a(1,6-NACM)	613	636 $[M + Na]^+$	437, 371, 255	16.46
17a(1,6-SG)	743	766 $[M + Na]^+$	437, 371, 255	11.85
19a(1,8-ME)	514	514 $[M]^+$	449, 438, 373, 270	14.12, 15.84
20a(1,8-NACM)	613	613 $[M]^+$	548, 438, 373, 270	13.95, 15.79
21a(1,8-SG)	743	743 $[M]^+$	456, 373, 280	8.41, 9.39
15b(1,6-ME)	530	553 $[M + Na]^+$	453, 387, 267	14.11
16b(1,6-NACM)	629	652 $[M + Na]^+$	453, 387, 267	14.03
17b(1,6-SG)	759	782 $[M + Na]^+$	453, 387, 267	10.41
19b(1,8-ME)	530	530 $[M]^+$	465, 454, 389, 286	12.50, 12.96
20b(1,8-NACM)	629	629 $[M]^+$	564, 454, 389, 286	12.50, 13.10
21b(1,8-SG)	759	759 $[M]^+$	456, 373, 280	8.55, 8.92

Table S5. In Vitro testing results for **3b** from the NCI/DTP, data from one experiment shown, maximum concentration: 100 μM, after 48 h incubation.

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : 775548 / 1	Experiment ID : 1311NS86	Test Type : 08	Units : Molar
Report Date : January 14, 2014	Test Date : November 12, 2013	QNS :	MC :
COMI : P53 (130859)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y9M	

			Log10 Concentration												
	Time		Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.539	1.738	1.768	1.386	0.797	0.555	0.363	102	71	22	1	-33	2.63E-7	1.09E-5	> 1.00E-4
HL-60(TB)	0.667	2.727	2.633	2.218	0.957	0.574	0.553	95	75	14	-14	-17	2.59E-7	3.18E-6	> 1.00E-4
MOLT-4	0.612	2.258	2.373	2.165	1.267	0.653	0.411	107	94	40	2	-33	6.49E-7	1.18E-5	> 1.00E-4
RPMI-8226	0.957	2.275	2.273	1.846	1.392	0.630	0.815	100	67	33	-34	-15	3.21E-7	3.10E-6	> 1.00E-4
SR	0.252	1.046	1.078	0.681	0.396	0.225	0.207	104	54	18	-11	-18	1.29E-7	4.24E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.398	1.457	1.480	1.400	0.572	0.065	0.113	102	95	16	-84	-72	3.72E-7	1.46E-6	4.61E-6
HOP-62	0.830	1.766	1.729	1.644	1.111	0.365	0.162	96	87	30	-56	-80	4.45E-7	2.23E-6	8.50E-6
HOP-92	0.944	1.443	1.412	1.294	1.192	0.882	0.270	94	70	50	-7	-71	9.67E-7	7.63E-6	4.67E-5
NCI-H226	0.851	2.259	2.196	2.113	1.511	0.568	0.816	96	90	47	-33	-4	8.46E-7	3.84E-6	> 1.00E-4
NCI-H23	0.672	2.033	2.001	1.555	0.816	0.236	0.205	98	65	11	-65	-70	1.88E-7	1.38E-6	6.35E-6
NCI-H322M	0.888	2.233	2.256	2.307	2.069	0.188	0.139	102	105	88	-79	-84	1.69E-6	3.36E-6	6.71E-6
NCI-H460	0.386	3.254	3.272	2.813	0.692	0.189	0.208	101	85	11	-51	-46	2.94E-7	1.49E-6	.
NCI-H522	1.103	2.174	2.130	1.979	1.748	0.390	0.547	96	82	60	-65	-50	1.21E-6	3.03E-6	7.63E-6
Colon Cancer															
COLO 205	0.527	1.435	1.372	1.213	0.817	0.102	0.118	93	76	32	-81	-78	3.84E-7	1.92E-6	5.33E-6
HCC-2998	0.568	1.953	1.951	1.893	1.299	0.072	0.113	100	96	53	-87	-80	1.05E-6	2.38E-6	5.41E-6
HCT-116	0.207	1.806	1.759	1.439	0.594	0.037	0.030	97	77	24	-82	-86	3.25E-7	1.69E-6	4.99E-6
HCT-15	0.284	2.269	2.050	1.878	1.008	0.037	0.075	89	80	36	-87	-74	4.91E-7	1.97E-6	5.02E-6
KM12	0.508	2.624	2.628	2.435	1.609	0.222	0.306	100	91	52	-56	-40	1.04E-6	3.02E-6	.
SW-620	0.314	2.596	2.439	1.538	1.138	0.759	0.160	93	54	36	19	-49	1.61E-7	1.92E-5	> 1.00E-4
CNS Cancer															
SF-268	0.564	1.893	1.914	1.680	0.944	0.498	0.250	102	84	29	-12	-56	4.11E-7	5.12E-6	7.40E-5
SF-295	0.641	2.647	2.362	1.926	0.929	0.482	0.136	86	64	14	-25	-79	1.92E-7	2.32E-6	2.92E-5
SF-539	0.954	2.577	2.321	1.419	0.866	0.242	0.312	84	29	-9	-75	-67	4.13E-8	5.69E-7	4.20E-6
SNB-19	0.705	2.184	2.137	1.881	1.240	0.992	0.167	97	80	36	19	-76	4.79E-7	1.59E-5	5.30E-5
SNB-75	0.763	1.515	1.271	1.266	1.102	0.781	0.217	68	67	45	2	-72	5.91E-7	1.08E-5	5.11E-5
U251	0.597	1.836	1.787	1.374	0.921	0.573	0.016	96	63	26	-4	-97	2.22E-7	7.36E-6	3.11E-5
Melanoma															
LOX IMVI	0.316	2.162	2.172	1.607	0.477	0.003	0.083	101	70	9	-99	-74	2.11E-7	1.20E-6	3.51E-6
M14	0.452	1.732	1.539	0.873	0.252	0.180	0.060	85	33	-44	-60	-87	4.69E-8	2.67E-7	2.26E-6
MDA-MB-435	0.554	2.500	2.188	1.953	1.450	0.387	0.077	84	72	46	-30	-86	7.03E-7	4.01E-6	2.26E-5
SK-MEL-2	1.069	2.220	2.200	2.108	2.026	0.341	0.246	98	90	83	-68	-77	1.66E-6	3.55E-6	7.59E-6
SK-MEL-28	0.627	1.859	1.817	1.786	1.484	0.189	0.218	97	94	70	-70	-65	1.38E-6	3.15E-6	7.20E-6
SK-MEL-5	0.621	2.475	2.300	1.460	0.971	0.021	0.135	91	45	19	-97	-78	7.85E-8	1.46E-6	3.95E-6
UACC-257	1.042	2.044	2.039	1.985	1.723	0.575	0.051	100	94	68	-45	-95	1.44E-6	4.00E-6	1.27E-5
UACC-62	0.774	2.948	2.709	1.815	0.747	0.112	0.119	89	48	-4	-86	-85	8.88E-8	8.53E-7	3.69E-6
Ovarian Cancer															
IGROV1	0.763	2.332	2.422	2.188	1.822	0.940	0.487	106	91	67	11	-36	2.05E-6	1.73E-5	> 1.00E-4
OVCAR-3	0.513	1.625	1.693	1.524	1.246	0.057	0.091	106	91	66	-89	-82	1.27E-6	2.66E-6	5.60E-6
OVCAR-4	0.665	1.455	1.267	1.241	1.177	0.072	0.447	76	73	65	-89	-33	1.25E-6	2.64E-6	.
OVCAR-5	0.693	1.466	1.377	1.456	1.004	0.101	0.137	88	99	40	-85	-80	6.80E-7	2.09E-6	5.22E-6
OVCAR-8	0.632	2.173	2.135	1.772	1.001	0.396	0.389	98	74	24	-37	-38	3.01E-7	2.46E-6	> 1.00E-4
NCI/ADR-RES	0.494	1.778	1.775	1.392	0.743	0.268	0.376	100	70	19	-46	-24	2.48E-7	1.99E-6	> 1.00E-4
SK-OV-3	0.933	1.588	1.605	1.523	1.217	0.746	0.044	103	90	43	-20	-95	7.22E-7	4.82E-6	2.50E-5
Renal Cancer															
786-0	0.506	1.836	1.722	0.913	0.563	0.278	0.099	91	31	4	-45	-80	4.80E-8	1.22E-6	1.38E-5
A498	1.386	2.302	2.168	1.757	1.543	1.055	0.050	85	41	17	-24	-96	6.14E-8	2.61E-6	2.29E-5
ACHN	0.448	1.858	1.713	0.612	0.593	0.417	0.171	90	12	10	-7	-62	3.22E-8	3.92E-6	6.06E-5
CAKI-1	0.613	2.544	2.362	1.542	1.090	0.575	0.038	91	48	25	-6	-94	9.01E-8	6.30E-6	3.16E-5
RXF 393	0.735	1.356	1.270	1.070	0.928	0.388	0.162	86	54	31	-47	-78	1.49E-7	2.50E-6	1.23E-5
SN12C	0.945	3.097	3.034	2.830	1.604	0.146	0.177	97	88	31	-85	-81	4.57E-7	1.84E-6	5.01E-6
TK-10	0.971	2.136	2.144	1.972	1.938	1.184	0.118	101	86	83	18	-88	3.23E-6	1.49E-5	4.40E-5
UO-31	0.831	2.325	2.325	1.793	1.419	1.142	0.250	100	64	39	21	-70	3.75E-7	1.70E-5	6.03E-5
Prostate Cancer															
PC-3	0.671	1.471	1.379	1.260	1.107	0.097	0.119	88	74	54	-86	-82	1.08E-6	2.45E-6	5.57E-6
DU-145	0.354	1.477	1.556	1.272	0.512	0.057	0.029	107	82	14	-84	-92	2.94E-7	1.39E-6	4.50E-6
Breast Cancer															
MCF7	0.349	1.995	1.677	1.263	0.682	0.068	0.159	81	55	20	-81	-55	1.43E-7	1.59E-6	4.97E-6
MDA-MB-231/ATCC	0.612	1.415	1.433	1.315	1.209	0.294	0.346	102	88	74	-52	-44	1.56E-6	3.88E-6	.
HS 578T	1.009	2.181	2.099	2.040	1.865	0.750	0.942	93	88	73	-26	-7	1.71E-6	5.49E-6	> 1.00E-4
BT-549	0.820	1.638	1.423	1.345	1.236	0.415	0.130	74	64	51	-49	-84	1.02E-6	3.22E-6	1.04E-5
T-47D	0.857	1.493	1.414	1.343	1.103	0.638	0.426	88	76	39	-26	-50	4.98E-7	3.99E-6	9.68E-5
MDA-MB-468	0.681	1.239	1.212	1.206	1.077	0.258	0.175	95	94	71	-62	-74	1.44E-6	3.41E-6	8.11E-6

Table S6. Antiproliferative effects (mean-graph midpoint) of **2b**, **3b**, tamoxifen and cisplatin in the NCI-60 screen.

Compound	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)
2b	0.52	4.28	22.9
3b	0.40	3.19	18.3
Tamoxifen [a]	4.31	11.7	31.3
Cisplatin [a]	15	58.4	92.5

(a) The data of tamoxifen and cisplatin from NCI/DTP screening, June 2016, maximum concentration: 100 μM, after 48 h incubation.

Supplementary References

(1) Y. Wang, P. Pigeon, S. Top, M. J. McGlinchey, and G. Jaouen, *Angew. Chem. Int. Ed.* **2015**, *54*, 10230-10233.

(2) D. Y. Curtin, R. J. Harder, *J. Am. Chem. Soc.* **1960**, *82*, 2357-2368.

(3) G. M. Sheldrick, *Acta Cryst. A* **2008**, *64*, 112-122.

(4) L. J. Farrugia, *J. Appl. Cryst.* **1999**, *32*, 837-838.

(5) P. Kremers, P. Beaune, T. Cresteil, J. de Graeve, S. Columelli, J. P. Leroux, J. E. Gielen. *Eur. J. Biochem.* **1981**, *118*(3), 599-606.