Supporting Information

Platinum(II) O,S complexes as potential metallodrugs against Cisplatin resistance

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Synthesis and Spectroscopic Data of Compounds **L1-L12**

General procedure 1: β-hydroxy dithiocinnamic acid alkyl esters (L1-L12).
In case of a hydroxy-β-hydroxy dithiocinnamic acid alkyl ester, a mixture of the hydroxy-acetophenone derivate (1 equiv) and imidazole (2 equiv) in dimethylformamide (DMF, 50 ml) was dropped to a solution of *tert.*-butyldimethylchlorosilan (1 equiv) in DMF (25 ml). After stirring for 20 h at room temperature an aqueous solution of sodium hydrogen carbonate (200 ml) was added to the reaction mixture and the evolving two-phased system was seperated. The aquatic phase was extracted with hexane (3x20 ml) and the combined organic solutions washed with water (3x20 ml) followed by drying with sodium sulfate, filtration and evaporation of the solvent.
In a second step to a solution of potassium-*tert.*-butoxylate (*t*-BuOK, 2 equiv) in diethyl ether (250 ml), cooled down at -70°C, was dropped the corresponding acetophenone derivate (1 equiv) in diethyl ether (50 ml). Carbon disulfide (CS_2, 1.4 equiv) was dropped to the solution and stirred one hour at -70°C. After warming up the reaction mixture was stirred two hours at room temperature. Alkyl halide (1 equiv) was added and the mixture stirred for 15 h. Solvent was removed and dichlormethane (100 ml) was added to the oil. Sulfuric acid (aqueous solution, 2M, 100 ml) was added to the suspension and stirred for 30 minutes at room temperature. The two-phased system was seperated and the aqueous phase extracted with dichlormethane (3x35 ml). The combined organic phases were washed with water (3x20 ml), dried with sodium sulfate, followed by filtration and evaporation of the solvent. The crude product was purified with column cromatography.
Last step is the deprotection of the TBDMS-protection group in case of hydroxy-β-hydroxy dithiocinnamic acid alkyl esters. The β-hydroxy dithiocinnamic alkyl ester (1equiv) is solved in tetrahydrofurane (THF, 60 ml) and tetra-n-butylammonium flouride (TBAF, 2 equiv, 1M in THF) was dropped to the solution. After stirring for three days at room temperature sulfuric acid (50 ml, 2M) was added and stirred for four hours, followed by seperating the two phases. The aqueous phase was extracted with DCM (3x35 ml), combined organic phases were washed with water (3x20 ml), dried over sodium sulfate and filtrated. The crude product was purified with column cromatography.
Ligands **L1-L12** were prepared as described above or have been reported earlier.[1-2]

2'-Methoxy-β-hydroxy dithiocinnamic methyl ester (L1)
Synthesis was performed according to general procedure 1. The 2'-methoxyacetophenone (1.8 ml, 13.32 mmol) and CS_2 (1.13 ml, 18.64 mmol) was dropped to the *t*-BuOK (3.0 g, 27.00 mmol) solution. Methyliodide (0.83 ml, 27.00 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 1.21 g (37.8%) as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3H, -S-CH_3); 3.85 (s, 3H, -OCH_3); 6.90 (d, $^3J_{H-H}$=8.4 Hz, 1H, -Ar-*o*-H); 6.96 (ddd, $^3J_{H-H}$=7.6 Hz, $^4J_{H-H}$=1.0 Hz, 1H, -Ar-*m*-H); 7.20 (s, 1H, =CH); 7.36 (ddd, $^3J_{H-H}$=7.6 Hz, $^4J_{H-H}$=1.0 Hz, 1H, -Ar-*p*-H); 7.79 (dd, $^3J_{H-H}$=7.8 Hz, $^4J_{H-H}$=1.8 Hz, 1H, Ar-*m*-H); 15.08 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 17.1 (-S-CH_3); 55.8 (-OCH_3); 111.7 (-Ar-*o*-C); 112.9 (=CH); 120.8 (-Ar-*m*-C); 123.2 (-Ar-C1); 130.2 (-Ar-*m*-C); 133.8 (-Ar-*p*-C); 157.8 (-Ar-OCH_3); 167.6 (-C-OH); 217.2 (-C=S). MS (DEI): m/z = 242, 240, 209, 193, 135, 121, 92, 77. Elemental analysis: calculated for $C_{11}H_{12}O_2S_2$ C: 54.97%; H: 5.03%; S: 26.68%, found: C: 55.13%; H: 5.03%; S: 27.11%.

3'-Methoxy-β-hydroxy dithiocinnamic methyl ester (L2)
Synthesis was performed according to general procedure 1. The 3'-methoxyacetophenone (1.8 ml, 13.32 mmol) and CS_2 (1.13 ml, 18.64 mmol) were dropped to the *t*-BuOK (3.0 g, 27.00 mmol) solution. Methyliodide (0.83 ml, 27.00 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 2.14 g (66.9%) as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 3H, -S-CH_3); 3.89 (s, 3H, -OCH_3); 6.97 (s, 1H, =CH); 7.08 (dd, $^3J_{H-H}$=8.2 Hz, $^4J_{H-H}$=0.8 Hz, 1H, -Ar-*p*-H); 7.38 (t, 1H, -Ar-*m*-H); 7.44 (m, 1H, -Ar-*o*-H); 7.48 (m, 1H, -Ar-*o*-H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 17.2 (-S-CH_3); 55.5 (-OCH_3); 111.8 (-Ar-*o*-C); 112.9 (=CH); 117.9 (-Ar-*o*-C); 120.3 (-Ar-*m*-C); 121.6 (-Ar-C1); 135.7 (-Ar-*p*-C); 159.9 (-Ar-OCH_3); 169.1 (-C-OH); 217.3 (-C=S). MS (DEI): m/z = 240, 225, 209, 193, 135, 121, 92, 77. Elemental analysis: calculated for $C_{11}H_{12}O_2S_2$ C: 54.97%; H: 5.03%; S: 26.68%, found: C: 55.23%; H: 5.07%; S: 27.01%.

4'-Methoxy-β-hydroxy dithiocinnamic methyl ester(L3).
Synthesis was performed according to general procedure 1. The 4'-methoxyacetophenone (2 g, 13.32 mmol) and CS_2 (1.13 ml, 18.64 mmol) were dropped to the *t*-BuOK (3.0 g, 27.00 mmol) solution. Methyliodide (0.83 ml, 13.32 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 1.26 g (39.4%) as yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.68 (s, 3H, -S-CH_3); 3.89 (s, 3H, -OCH_3); 6.98 (m, 3H, -Ar-*o*-H/=CH); 7.89 (d, $^3J_{H-H}$=9.0 Hz, 2H, -Ar-*m*-H); 15.21 (-C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 17.0 (-S-CH_3); 55.5 (-OCH_3); 107.1 (=CH); 126.2 (-Ar-*o*-C); 128.7 (-Ar-C1); 129.0 (-Ar-*m*-C); 131.4 (-Ar-*m*-C); 157.8 (-Ar-OCH_3); 169.6 (-C-OH); 215.7 (-C=S).MS (DEI): m/z = 241, 240, 225, 193, 135, 121, 92.
Elemental analysis: calculated for $C_{11}H_{12}O_2S_2$ C: 54.97%; H: 5.03%; S: 26.68%, found: C: 55.25%; H: 5.08%; S: 27.13%.

2'-Methoxy-β-hydroxy dithiocinnamic ethyl ester (L4).
Synthesis was performed according to general procedure 1. The 2'-methoxyacetophenone (2.3 ml, 16.65 mmol) and CS_2 (1.40 ml, 23.31 mmol) were dropped to the *t*-BuOK (3.7 g, 33.23 mmol) solution. Ethyliodide (1.34 ml, 16.65 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 2.51 g (59.3%) as orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, 3H, -S-CH_2-CH_3); 3.24 (q, 2H, -S-CH_2-); 3.88 (s, 3H, -OCH_3); 6.94 (d, $^3J_{H-H}$=8.5 Hz, 1H, -Ar-*o*-H); 6.96 (ddd, $^3J_{H-H}$=7.6 Hz, $^4J_{H-H}$=1.0 Hz, 1H, -Ar-*m*-H); 7.23 (s, 1H, =CH); 7.41 (ddd, $^3J_{H-H}$=7.96 Hz, $^4J_{H-H}$=1.0 Hz, 1H, -Ar-*p*-H); 7.79 (dd, $^3J_{H-H}$=7.8 Hz, $^4J_{H-H}$=1.8 Hz, 1H, Ar-*m*-H); 15.21 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 12.8 (-S-CH_2-CH_3); 27.7 (-S-CH_2-); 55.6 (-OCH_3); 111.6 (-Ar-*o*-C); 112.8 (=CH); 120.7 (-Ar-*m*-C); 123.1 (-Ar-C1); 130.0 (-Ar-*m*-C); 132.5 (-Ar-*p*-C); 157.7 (-Ar-OCH_3); 167.8 (-C-OH); 216.3 (-C=S). MS (DEI): m/z = 256, 254, 223, 193, 135, 121, 92, 77. Elemental analysis: calculated for $C_{11}H_{14}O_2S_2$ C: 56.66%; H: 5.55%; S: 25.21%, found: C: 57.02%; H: 5.60%; S: 25.68%.

3'-Methoxy-β-hydroxy dithiocinnamic ethyl ester (L5).
Synthesis was performed according to general procedure 1. The 3'-methoxyacetophenone (1.8 ml, 13.32 mmol) and CS_2 (1.13 ml, 18.65 mmol) were dropped to the *t*-BuOK (3.0 g, 27.00 mmol) solution. Ethyliodide (1.07 ml, 13.32 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 2.89 g (85.5%) as orange oil.^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 3H, -S-CH_2-CH_3); 3.29 (q, 2H, -S-CH_2-); 3.86 (s, 3H, -OCH_3); 6.91 (s, 1H, =CH); 7.06 (dd, $^3J_{H-H}$=8.2 Hz, $^4J_{H-H}$=0.8 Hz, 1H, -Ar-*p*-H); 7.38 (t, 1H, -Ar-*m*-H); 7.44 (m, 2H, -Ar-*o*-H); 15.18 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 12.8 (-S-CH_2-CH_3); 27.9 (-S-CH_2-); 55.4 (-OCH_3); 111.8 (-Ar-*o*-C); 112.9 (=CH); 117.8 (-Ar-*o*-C); 120.2 (-Ar-*m*-C); 121.6 (-Ar-C1); 135.7 (-Ar-*p*-C); 159.9 (-Ar-OCH_3); 169.4 (-C-OH); 217.3 (-C=S). MS (DEI): m/z = 255, 254, 225, 193, 135, 121, 92, 77. Elemental analysis: calculated for $C_{11}H_{14}O_2S_2$ C: 56.66%; H: 5.55%; S: 25.21%, found: C: 56.53%; H: 5.48%; S: 25.26%.

4'-Methoxy-β-hydroxy dithiocinnamic ethyl ester (L6).
Synthesis was performed according to general procedure 1. The 4'-methoxyacetophenone (2.0 g, 13.32 mmol) and CS_2 (1.13 ml, 18.65 mmol) were dropped to the *t*-BuOK (3.0 g, 27.00 mmol) solution. Ethyliodide (1.07 ml, 13.32 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 2.64 g (78.1%) as yellow crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.40 (t, 3H, -S-CH_2-CH_3); 3.29 (q, 2H, -S-CH_2-); 3.89 (s, 3H, -OCH_3); 6.91 (s, 1H, =CH); 6.97 (d, $^3J_{H-H}$=9.0 Hz, 2H, -Ar-*o*-H); 7.88 (d, $^3J_{H-H}$=9.0 Hz, 2H, -Ar-*m*-H); 15.21 (-C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 13.1 (-S-CH_2-CH_3); 27.7 (-S-CH_2-); 55.5 (-OCH_3); 107.1 (=CH); 126.3 (-Ar-*o*-C); 128.7 (-Ar-C1); 129.0 (-Ar-*m*-C); 131.4 (-Ar-*m*-C); 157.8 (-Ar-OCH_3); 169.9 (-C-OH); 214.9 (-C=S). MS (DEI): m/z = 254, 226, 193, 135, 92, 77. Elemental analysis: calculated for $C_{11}H_{14}O_2S_2$ C: 56.66%; H: 5.55%; S: 25.21%, found: C: 56.93%; H: 5.62%; S: 25.56%.

3'-Hydroxy-β-hydroxy dithiocinnamic methyl ester(L7).
Synthesis was performed according to general procedure 1. 3'-Hydroxy-acetophenone (8.2 g, 59.90 mmol) was protected with TBDMS (9.0 g, 59.90 mmol) and imidazole (8.16 g, 119.89 mmol) was used. Yield: 11.91 g (79.4%) as white oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.1 (s, 6H, -Si-$(CH_3)_2$); 0.78 (s, 9H, -C-$(CH_3)_3$); 2.34 (s, 3H -CH_3); 6.81 (dd, $^3J_{H-H}$=8.1 Hz, 1H, -Ar-*p*-H); 6.82 (t, ^{1}H, -Ar-*m*-H); 7.07 (s, 1H, -Ar-*o*-H); 7.11 (d, $^3J_{H-H}$=7.7 Hz 1H, -Ar-*o*-H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = -4.6 (-Si-$(CH_3)_2$); 18.0 (q, -C-

($CH_3)_3$); 25.5 (-C-($CH_3)_3$); 26.5 (-CH_3); 119.3 (-Ar-*o*-C); 121.4 (-Ar-*o*-C); 124.8 (-Ar-*p*-C); 129.4 (-Ar-*m*-C); 138.5 (-Ar-C1); 155.8 (-Ar-*m*-C-O-); 197.5 (-C=O). MS (ESI): m/z = 216, 184.
The 3'-TBDMS-acetophenone (5.0 g, 19.97 mmol) and CS_2 (1.70 ml, 27.95 mmol) were dropped to the *t*-BuOK (4.5 g, 39.93 mmol) solution. Methyliodide (1.30 ml, 19.97 mmol) was used. Column chromatography mobile phase: DCM 2:hexane 1. Yield: 3.52 g (51.7%) as green crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.21 (s, 6H, -Si-($CH_3)_2$); 0.98 (s, 9H, -C-($CH_3)_3$); 2.64 (s, 3H, -S-CH_3); 6.90 (s, 1H, =CH); 6.96 (dd, $^3J_{H\text{-}H}$=8.1 Hz, 1H, -Ar-*p*-H); 7.28 (t, 1H, -Ar-*m*-H); 7.33 (s, 1H, -Ar-*o*-H); 7.43 (d, $^3J_{H\text{-}H}$=7.7 Hz, 1H, -Ar-*o*-H); 15.05 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = -4.2 (-Si-($CH_3)_2$); 17.1 (q, -C-($CH_3)_3$); 18.2 (-C-($CH_3)_3$); 31.6 (-CH_3); 107.9 (=CH); 118.3 (-Ar-*o*-C); 119.6 (-Ar-*o*-C); 123.6 (-Ar-*p*-C); 129.7 (-Ar-*m*-C); 135.7 (-Ar-C1); 156.1 (-Ar-*m*-C-O-); 169.1 (-C-OH); 217.2 (-C=S). MS (DEI): m/z = 341, 340, 293, 235.
The 3'-TBDMS-β-hydroxy dithiocinnamic methyl ester (3.5 g, 10.3 mmol) was deprotected with TBAF (20.7 ml, 20.7 mmol). Column chromatography mobile phase: hexane 2:DCM 1 - hexane 1 : DCM 1 - hexane 1 : DCM 3. Yield: 1.89 g (81.1%) as yellow crystals. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.65 (s, 3H, -S-CH_3); 6.96 (s, 1H, =CH); 7.03 (dd, $^3J_{H\text{-}H}$=8.2 Hz, $^4J_{H\text{-}H}$=0.8 Hz, 1H, -Ar-*p*-H); 7.29 (t, 1H, -Ar-*m*-H); 7.33 (s, 1H, -Ar-*o*-H); 7.39 (d, $^3J_{H\text{-}H}$=8.2 Hz, 1H, -Ar-*o*-H); 15.09 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 17.4 (-CH_3); 108.2 (-Ar-*o*-C); 113.8 (=CH); 118.8 (-Ar-*o*-C); 119.5 (-Ar-C1); 130.3 (-Ar-*m*-C); 135.9 (-Ar-*p*-C); 157.1 (-Ar-C-OH); 169.3 (-C-OH); 217.8 (-C=S). MS (DEI): m/z = 226, 179, 121.Elemental analysis: calculated for $C_{10}H_{10}O_2S_2$ C: 53.07%; H: 4.45%; S:28.34%, found: C: 52.99%; H: 4.55%; S: 27.74%.

4'-Hydroxy-β-hydroxy dithiocinnamic methyl ester(L8).
Synthesis was performed according to general procedure 1. 4'-Hydroxy-acetophenone (8.2 g, 59.90 mmol) was protected with TBDMS (9.0 g, 59.90 mmol) and imidazole (8.16 g, 119.89 mmol) was used.
Yield: 18.73 g (100%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 6H, -Si-($CH_3)_2$); 0.96 (s, 9H, -C-($CH_3)_3$); 2.52 (s, 3H -CH_3); 8.84 (d, $^3J_{H\text{-}H}$=8.8 Hz, 2H, -Ar-*o*-H); 7.85 (d, $^3J_{H\text{-}H}$= 8.8 Hz 2H, -Ar-*m*-H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = -4.1 (-Si-($CH_3)_2$); 18.2 (q, -C-($CH_3)_3$); 25.6 (-C-($CH_3)_3$); 26.3 (-CH_3); 119.8 (-Ar-*o*-C); 130.5 (-Ar-*m*-C); 130.8 (-Ar-C1); 160.2 (-Ar-*p*-C-O-); 196.8 (-C=O). MS (ESI): m/z = 250, 193, 151.
The 4'-TBDMS-acetophenone (5.0 g, 19.97 mmol) and CS_2 (1.70 ml, 27.95 mmol) were dropped to the *t*-BuOK (4.5 g, 39.93 mmol) solution. Methyliodide (1.00 ml, 19.97 mmol) was used. Column chromatography mobile phase: DCM 2:hexane 1. Yield: 3.25 g (47.8%) as green crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.21 (s, 6H, -Si-($CH_3)_2$); 0.97 (s, 9H, -C-($CH_3)_3$); 2.63 (s, 3H, -S-CH_3); 6.87 (d, $^3J_{H\text{-}H}$=8.8 Hz, 2H, -Ar-*o*-H); 6.91 (s, 1H, =CH); 7.78 (d, $^3J_{H\text{-}H}$=8.8 Hz, 2H, -Ar-*m*-H); 15.15 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = -4.4 (-Si-($CH_3)_2$); 16.9 (-CH_3); 18.2 (q, -C-($CH_3)_3$); 25.6 (-C-($CH_3)_3$); 107.2 (=CH); 120.3 (-Ar-*m*-C); 126.8 (-Ar-*o*-C); 128.6 (-Ar-C1); 159.5 (-Ar-*p*-C-O-); 196.6 (-C-OH); 215.7 (-C=S). MS (EI): m/z = 341, 293, 235.
The 4'-TBDMS-β-hydroxy dithiocinnamic methyl ester (3.25 g, 9.54 mmol) was deprotected with TBAF (19.1 ml, 19.1 mmol). Column chromatography mobile phase: hexane 2:DCM 1 - hexane 1 : DCM 1 - hexane 1 : DCM 3. Yield: 2.16 g (90.7%) as yellow crystals. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.60 (s, 3H, -S-CH_3); 6.82 (d, $^3J_{H\text{-}H}$=9.0 Hz, 2H, -Ar-*o*-H); 6.88 (s, 1H, =CH); 7.75 (d, $^3J_{H\text{-}H}$=9.0 Hz, 2H, -Ar-*m*-H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 16.7 (-CH_3); 106.8 (=CH); 115.5 (-Ar-*o*-C); 126.1 (-Ar-C1); 128.7 (-Ar-*m*-C); 158.9 (-Ar-C-OH); 169.2 (-C-OH); 215.8 (-C=S). MS (DEI): m/z = 226, 179, 121. Elemental analysis: calculated for $C_{10}H_{10}O_2S_2$ C: 53.07%; H: 4.45%; S:28.34%, found: C: 53.52%; H: 4.52%; S: 28.27%.

3'-Hydroxy-β-hydroxy dithiocinnamic ethyl ester (L9).
Synthesis was performed according to general procedure 1, first step is similar to L7.
The 3'-TBDMS-acetophenone (5.0 g, 19.97 mmol) and CS_2 (1.70 ml, 27.95 mmol) was dropped to the *t*-BuOK (4.5 g, 39.93 mmol) solution. Ethyliodide (1.61 ml, 19.97 mmol) was used. Column chromatography mobile phase: DCM 2:hexane 1. Yield: 4.67 g (66.7%) as brown oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.22 (s, 6H, -Si-($CH_3)_2$); 0.99 (s, 9H, -C-($CH_3)_3$); 1.37 (t, 3H, -S-CH_2-CH_3); 3.25 q, 2H, -S-CH_2-); 6.85 (s, 1H, =CH); 6.96 (dd, $^3J_{H\text{-}H}$=8.1 Hz, 1H, -Ar-*p*-H); 7.27 (t, 1H, -Ar-*m*-H); 7.34 (s, 1H, -Ar-*o*-H); 7.43 (d, $^3J_{H\text{-}H}$=7.9 Hz, 1H, -Ar-*o*-H); 15.11 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = -4.4 (-Si-($CH_3)_2$); 12.9 (-S-CH_2-CH_3); 18.2 (q, -C-($CH_3)_3$); 25.6 (-C-($CH_3)_3$); 27.8 (-S-CH_2-); 107.9 (=CH); 118.2 (-Ar-*o*-C); 119.5 (-Ar-

o-C); 123.5 (-Ar-*p*-C); 129.6 (-Ar-*m*-C); 135.7 (-Ar-C1); 156.0 (-Ar-*m*-C-O-); 169.0 (-C-OH); 216.4 (-C=S). MS (EI): m/z = 354, 293, 235, 211.
The 3'-TBDMS-β-hydroxy dithiocinnamic ethyl ester (4.7 g, 13.2 mmol) was deprotected with TBAF (26.3 ml, 26.3 mmol). Column chromatography mobile phase: hexane 2:DCM 1 - hexane 1 : DCM 1 - hexane 1 : DCM 3. Yield: 3.14 g (81.1%) as brown oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.37 (t, 3H, -S-CH_2-CH_3); 3.26(q, 2H, -S-CH_2-); 6.91 (s, 1H, =CH); 7.04 (d, $^{3}J_{H-H}$=8.2 Hz, 1H, -Ar-*p*-H); 7.32 (t, 1H, -Ar-*m*-H); 7.34 (s, 1H, -Ar-*o*-H); 7.42 (d, $^{3}J_{H-H}$=8.2 Hz, 1H, -Ar-*o*-H); 15.14 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 13.0 (-S-CH_2-CH_3); 28.3 (-S-CH_2-); 108.2 (-Ar-*o*-C); 113.8 (=CH); 118.9 (-Ar-*o*-C); 119.5 (-Ar-C1); 130.3 (-Ar-*m*-C); 136.0 (-Ar-*p*-C); 156.9 (-Ar-C-OH); 169.6 (-C-OH); 217.1 (-C=S). MS (DEI): m/z = 301, 214, 211, 179. Elemental analysis: calculated for $C_{11}H_{12}O_2S_2$ C: 54.97%; H: 5.03%; S: 26.68%, found: C: 55.25%; H: 5.02%; S: 27.02%.

4'-Hydroxy-β-hydroxy dithiocinnamic ethyl ester (L10).
Synthesis was performed according to general procedure 1, first step is similar to L8.
The 4'-TBDMS-acetophenone (5.0 g, 19.97 mmol) and CS_2 (1.70 ml, 27.95 mmol) were dropped to the *t*-BuOK (4.5 g, 39.93 mmol) solution. Ethyliodide (1.60 ml, 19.97 mmol) was used. Column chromatography mobile phase: DCM 2:hexane 1. Yield: 3.47 g (48.9%) as green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (s, 6H, -Si-$(CH_3)_2$); 0.97 (s, 9H, -C-$(CH_3)_3$); 1.36 (q, 2H, -S-CH_2-CH_3); 3.25(q, 2H, -S-CH_2-); 6.86 (d, $^{3}J_{H-H}$=8.9 Hz, 2H, -Ar-*o*-H); 6.87 (s, 1H, =CH); 7.78 (d, $^{3}J_{H-H}$=8.8 Hz, 2H, -Ar-*m*-H); 15.19 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = -4.4 (-Si-$(CH_3)_2$); 13.0 (-S-CH_2-CH_3); 18.2 (q, -C-$(CH_3)_3$); 25.6 (-C-$(CH_3)_3$); 27.6 (-S-CH_2-); 107.2 (=CH); 120.3 (-Ar-*m*-C); 126.9 (-Ar-*o*-C); 128.6 (-Ar-C1); 159.5 (-Ar-*p*-C-O-); 196.9 (-C-OH); 214.9 (-C=S). MS (EI): m/z = 354, 293.
The 4'-TBDMS-β-hydroxy dithiocinnamic methyl ester (3.02 g, 8.52 mmol) was deprotected with TBAF (17.1 ml, 17.1 mmol). Column chromatography mobile phase: hexane 2:DCM 1 - hexane 1 : DCM 1 - hexane 1 : DCM 3. Yield: 2.05 g (91.2%) as brown oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.37 (t, 3H, -S-CH_2-CH_3); 3.26 (q, 2H, -S-CH_2-); 6.91 (s, 1H, =CH); 6.92 (d, $^{3}J_{H-H}$=9.0 Hz, 2H, -Ar-*o*-H); 7.81 (d, $^{3}J_{H-H}$=9.0 Hz, 2H, -Ar-*m*-H); 15.20 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): δ = 13.9 (-S-CH_2-CH_3); 27.8 (-CH_2-); 106.9 (=CH); 115.8 (-Ar-*o*-C); 126.0 (-Ar-C1); 128.9 (-Ar-*m*-C); 159.8 (-Ar-C-OH); 170.1 (-C-OH); 215.2 (-C=S). MS (DEI): m/z = 240, 179, 121. Elemental analysis: calculated for $C_{11}H_{12}O_2S_2$ C: 54.97%; H: 5.03%; S: 26.68%, found: C: 55.06%; H: 4.97%; S: 26.73%.

β-Hydroxy dithiocinnamic methyl ester (L11).
Synthesis was performed according to general procedure 1. Acetophenone (2.0 ml, 16.65 mmol) and CS_2 (1.41 ml, 23.30 mmol) were dropped to the *t*-BuOK (3.7 g, 33.23 mmol) solution. Methyliodide (1.04 ml, 17.00 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1.5. Yield: 0.19 g (5.4%) as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 1H, -S-CH_3); 6.89 (s, 1H, =CH); 7.38 (m, 3H, -Ar-*o*-H/ -Ar-*p*-H); 7.80 (m, 2H, -Ar-*m*-H); 15.02 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 17.1 (-S-CH_3); 107.8 (=CH); 126.7 (-Ar-C1); 128.7 (-Ar-*o*-C); 131.9 (-Ar-*m*-C); 135.0 (-Ar-*p*-C); 169.2 (-C-OH); 217.3 (-C=S). MS (EI): m/z = 240, 211, 210, 163, 135, 105, 91, 85, 77, 51, 45. Elemental analysis: calculated for $C_{11}H_{10}OS_2$ C: 57.11%; H: 4.79%; S: 30.49%, found: C: 57.50%; H: 4.77%; S: 31.01%.

β-Hydroxy dithiocinnamic ethyl ester (L12).
Synthesis was performed according to general procedure 1. Acetophenone (2.4 ml, 20.81 mmol) and CS_2 (1.80 ml, 29.13 mmol) were dropped to the *t*-BuOK (4.7 g, 41.62 mmol) solution. Ethyliodide (1.70 ml, 20.81 mmol) was used. Column chromatography mobile phase: DCM 1:hexane 1. Yield: 3.15 g (67%) as green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (-S-CH_2-CH_3); 3.27 (q, 2H, -S-CH_2-); 6.90 (s, 1H, =CH); 7.46 (m, 3H, -Ar-*o*-H/ -Ar-*p*-H); 7.86 (m, 2H, -Ar-*m*-H); 15.16 (s, 1H, -C-OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 12.8 (-S-CH_2-CH_3); 27.8 (-S-CH_2-); 107.7 (=CH); 126.5 (-Ar-C1); 128.6 (-Ar-*o*-C); 131.7 (-Ar-*m*-C); 134.1 (-Ar-*p*-C); 169.4 (-C-OH); 216.3 (-C=S).MS (EI): m/z = 227, 224, 196, 163, 134, 105, 91, 85, 77, 51. Elemental analysis: calculated for $C_{11}H_{12}OS_2$ C: 58.89%; H: 5.39%; S: 28.58%, found: C: 58.69%; H: 5.30%; S: 28.60%.

Additional molecular structures

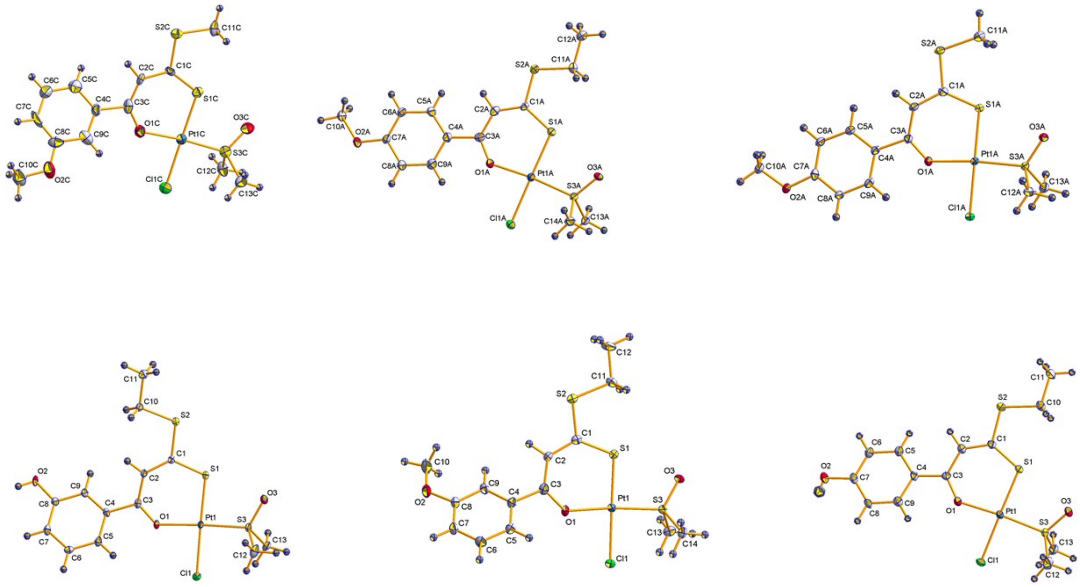


Figure S1. Molecular strucutres (50% propability) for **Pt2, Pt3, Pt5, Pt6, Pt9, Pt10**

Additional stability determinations

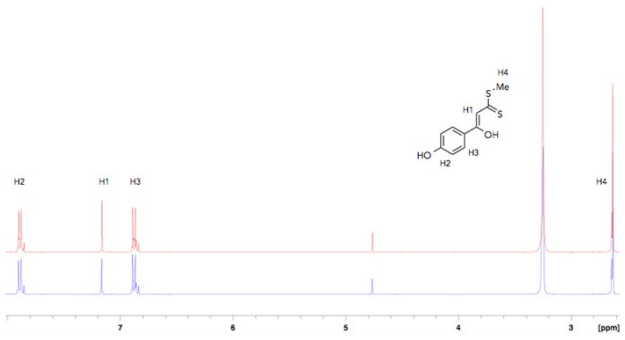
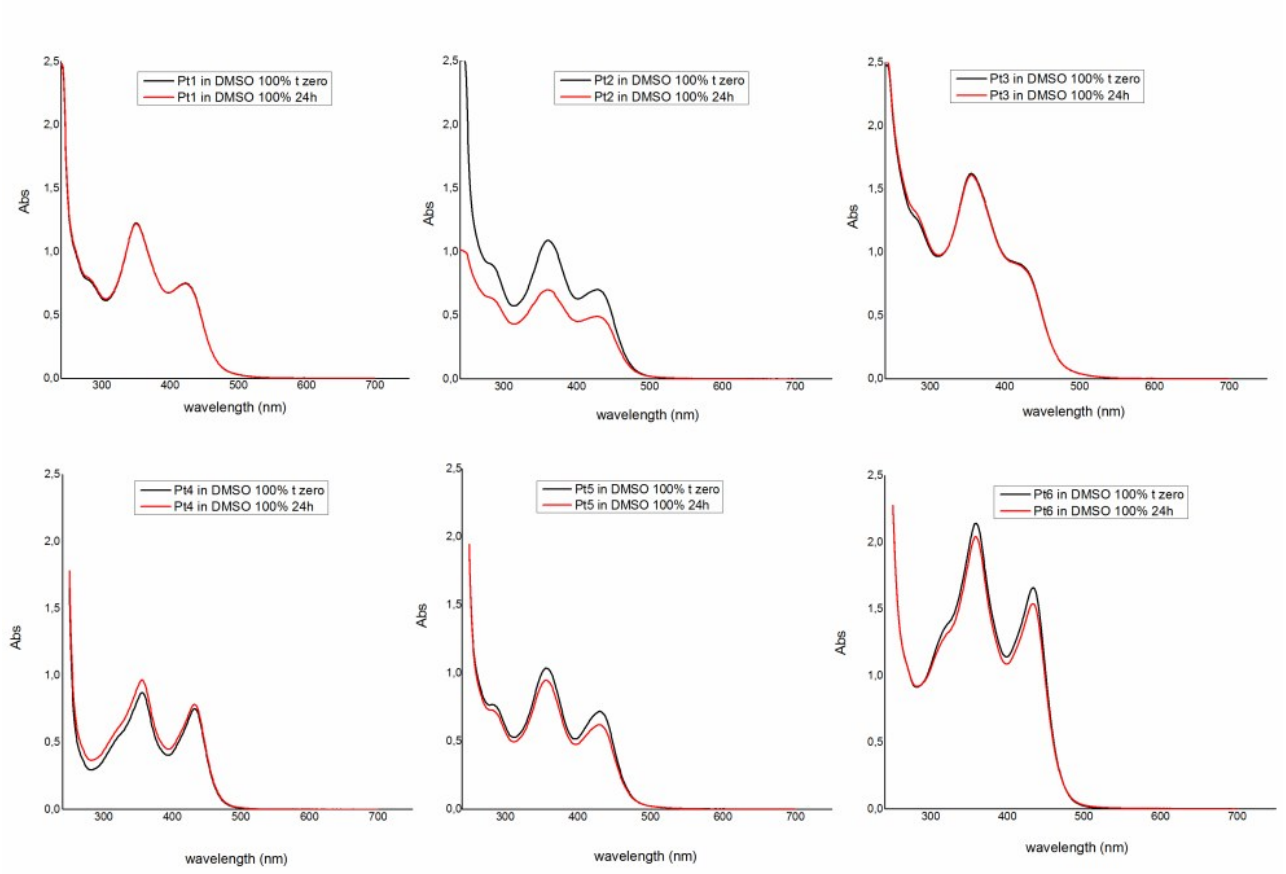
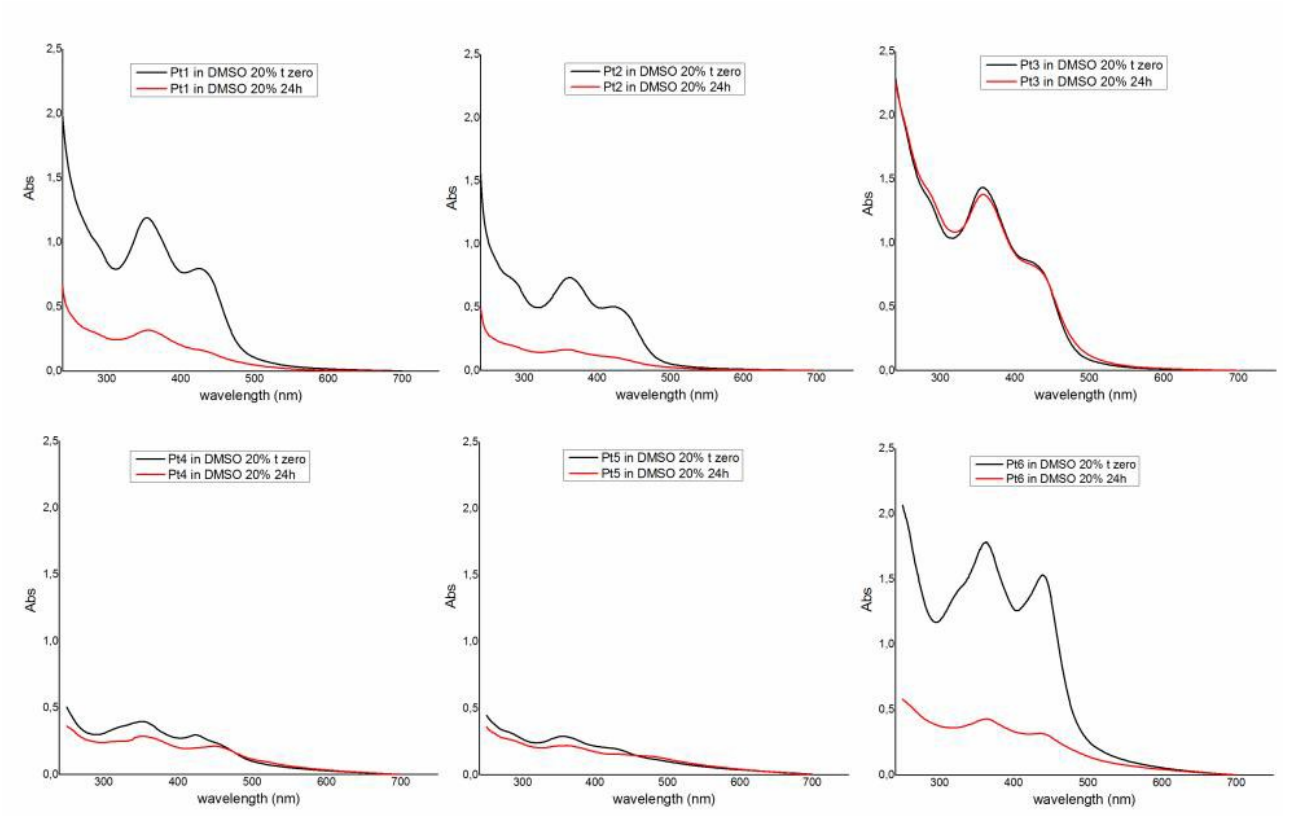


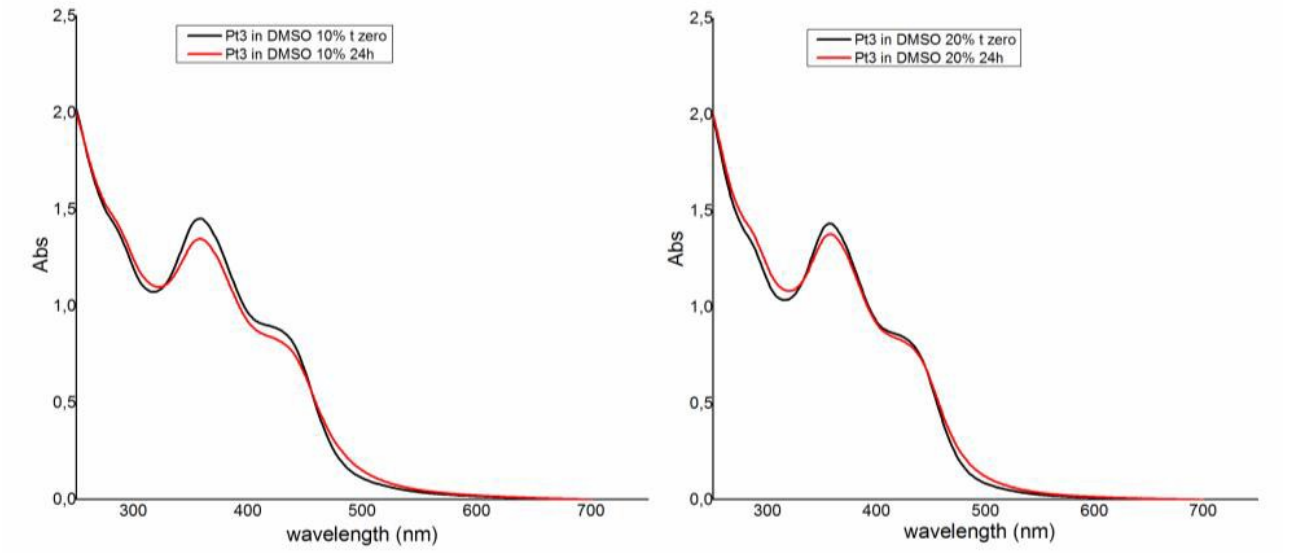
Figure S2. Stability determination of **L8** using ^{1}H NMR spectroscopy, Conditions: 600 MHz, 37 °C, dmso-d_6. Blue: first measurement (starting point), red: after 48 h. All compounds are stable under this conditions.



A

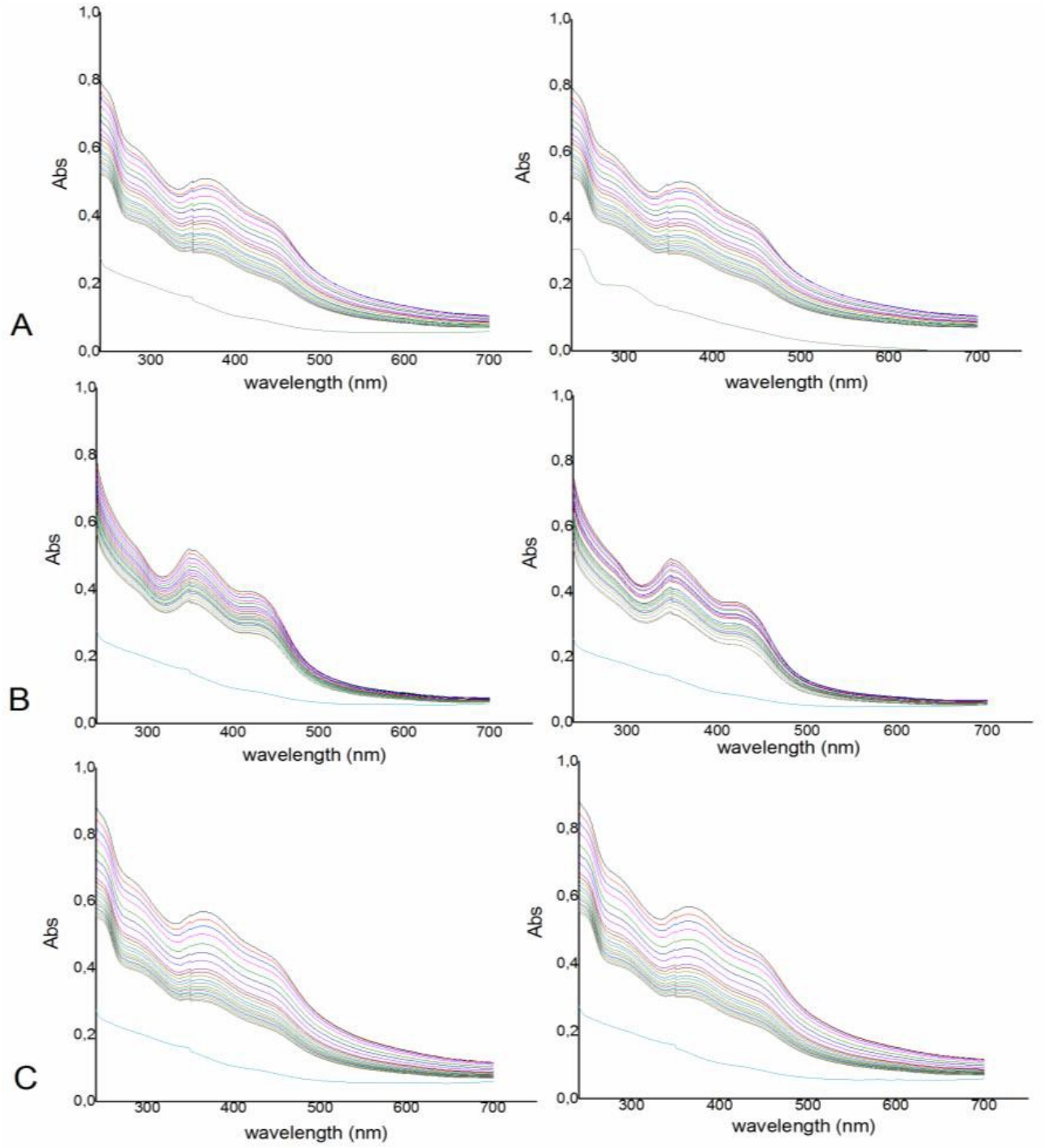


B



C

Figure S3. UV–visible spectra of compound **Pt1-Pt6** (1mM) in pure dmso (A) and in aqueous solutions containing 10% and 20% dmso (B). In panel C UV-Visible spectra of **Pt3** (1mM) in solution containing 10% and 20% dmso are reported. All spectra were collected after dissolution (black) and after 24 h of incubation (red).


A
B
C
Abs
wavelength (nm)
1,0
0,8
0,6
0,4
0,2
0,0
300
400
500
600
700

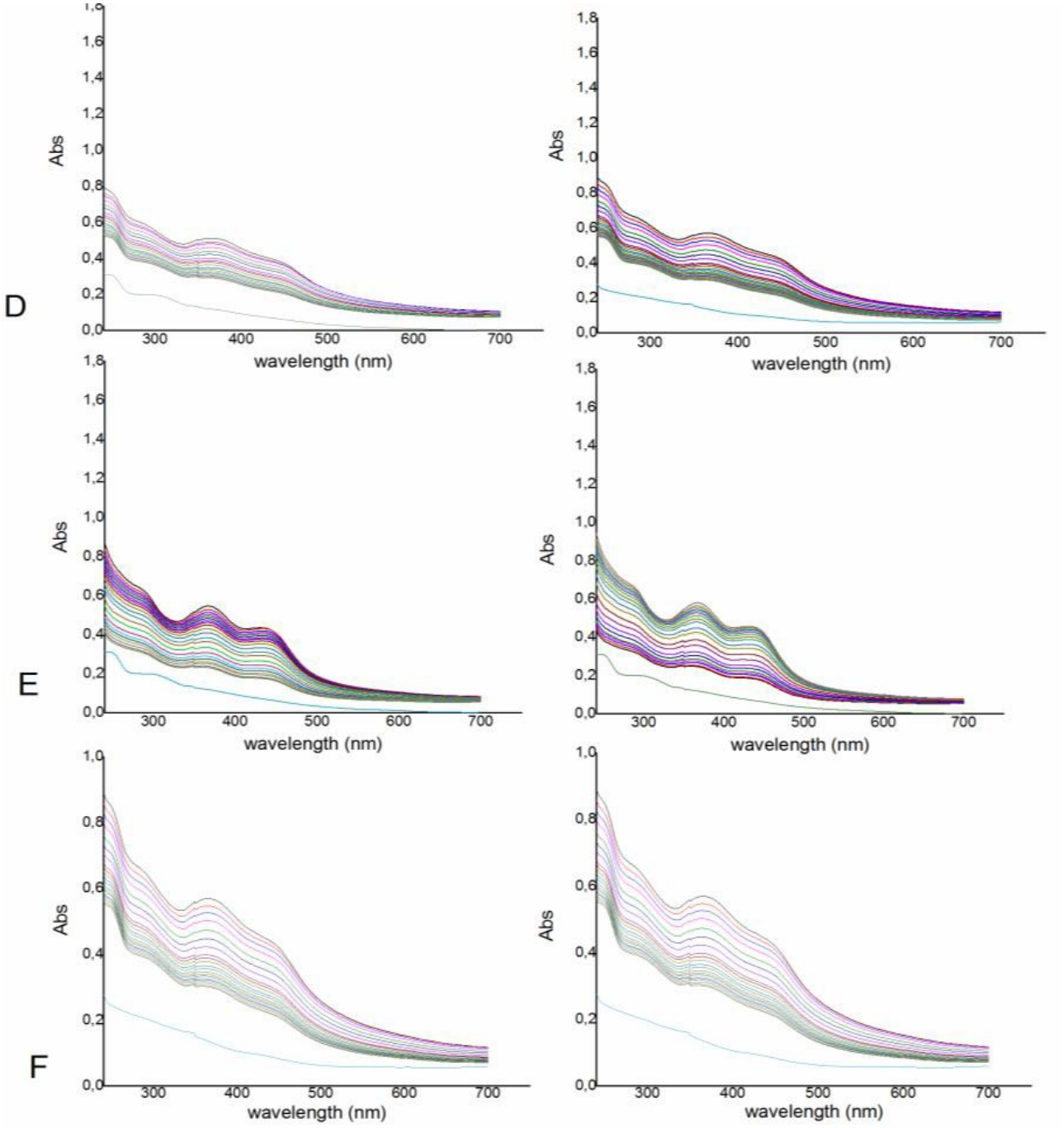


Figure S4. UV–visible spectra of 0.04 mM **Pt1-Pt6** (panels A…F) in 10 mM PBS pH 7.4 (left) and 0.9% NaCl (right) followed each 10 minutes for 3 hours and upon 24 h.

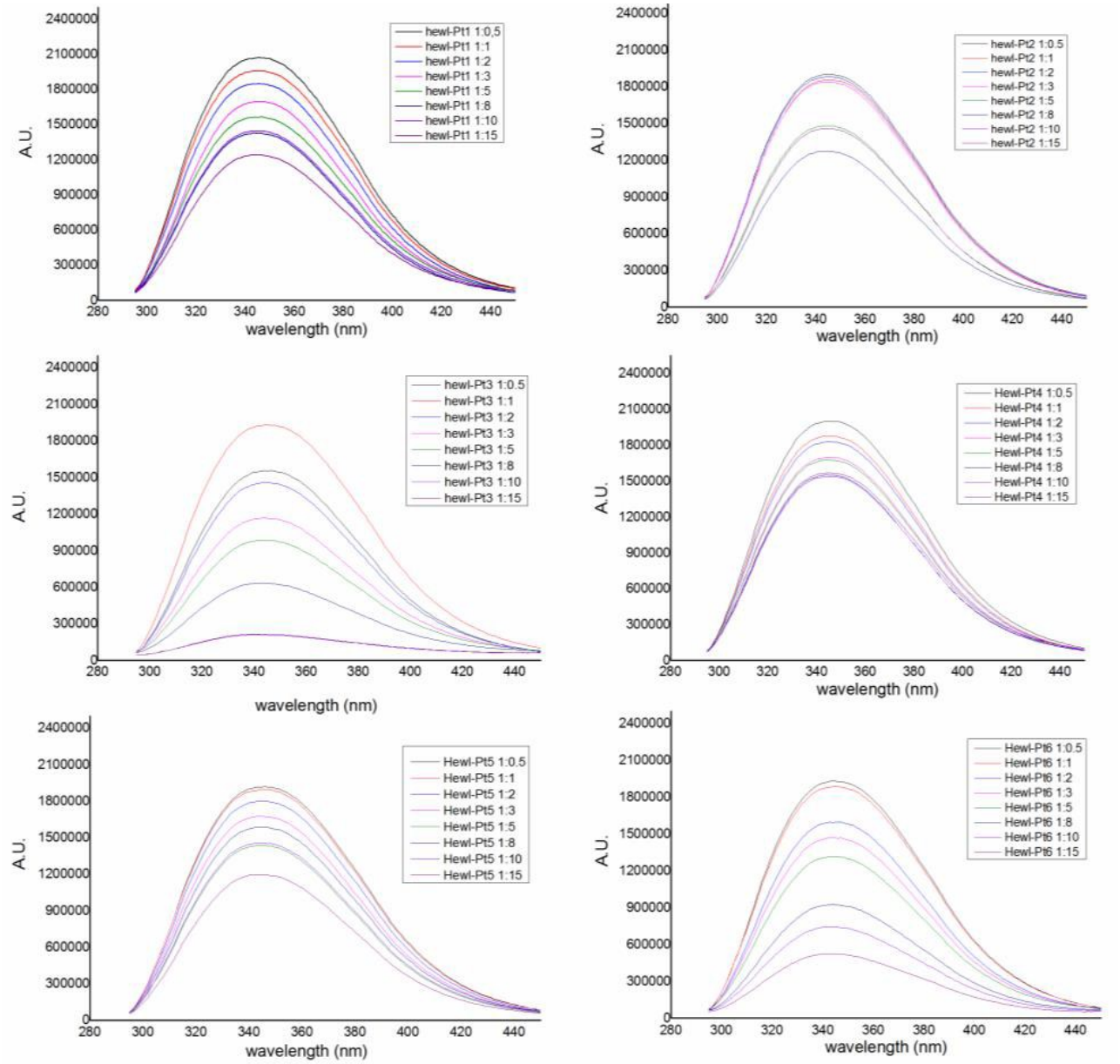


Figure S5. Fluorescence quenching spectra of HEWL (0.1 mg x mL-1) with different concentrations of **Pt1-Pt6** upon excitation at λ=280 nm at 300 K in 10 mM sodium acetate pH 4.4 (1.4% dmso) Spectra collected after excitation at λ=295 nm are reported in Figure S6.

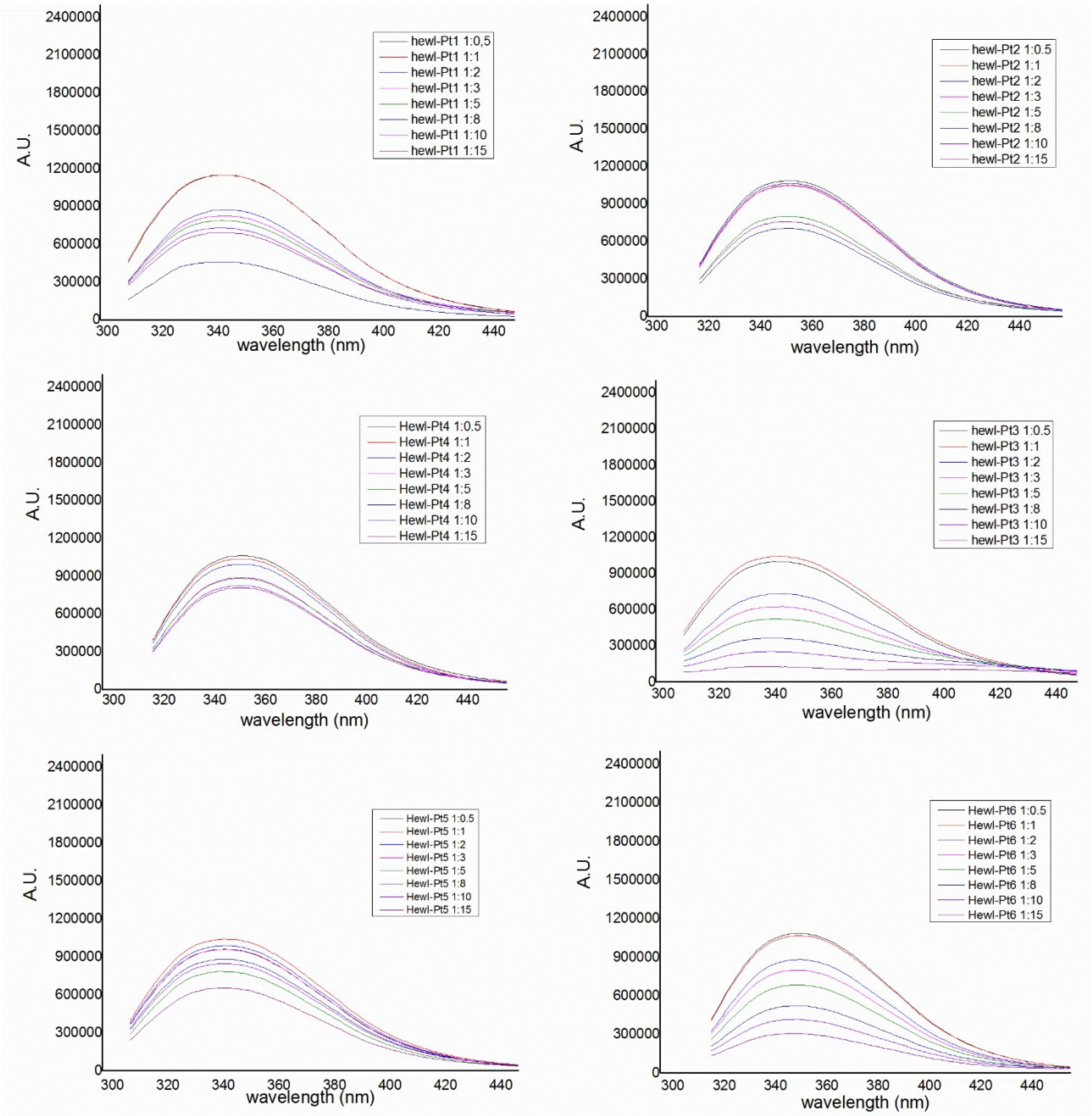


Figure S6. Fluorescence quenching spectra of HEWL (o.1 mg x mL -1) with different concentrations of Pt1-Pt6 upon excitation at 295 nm at 300 K in 10 mM sodium actetate pH 4.4 (1.4% dmso).

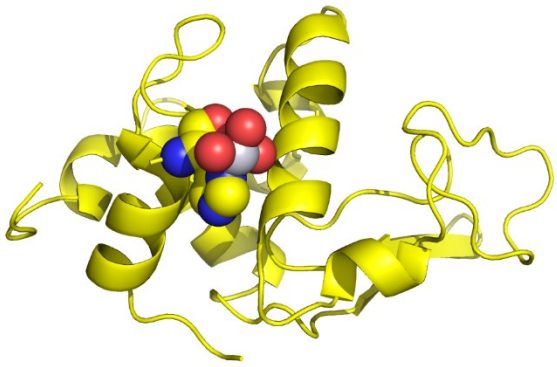


Figure S7. Cartoon representation of the HEWL-**Pt1** structure. The side chain of His15 and the Pt centre with its ligands are also shown as sphere.

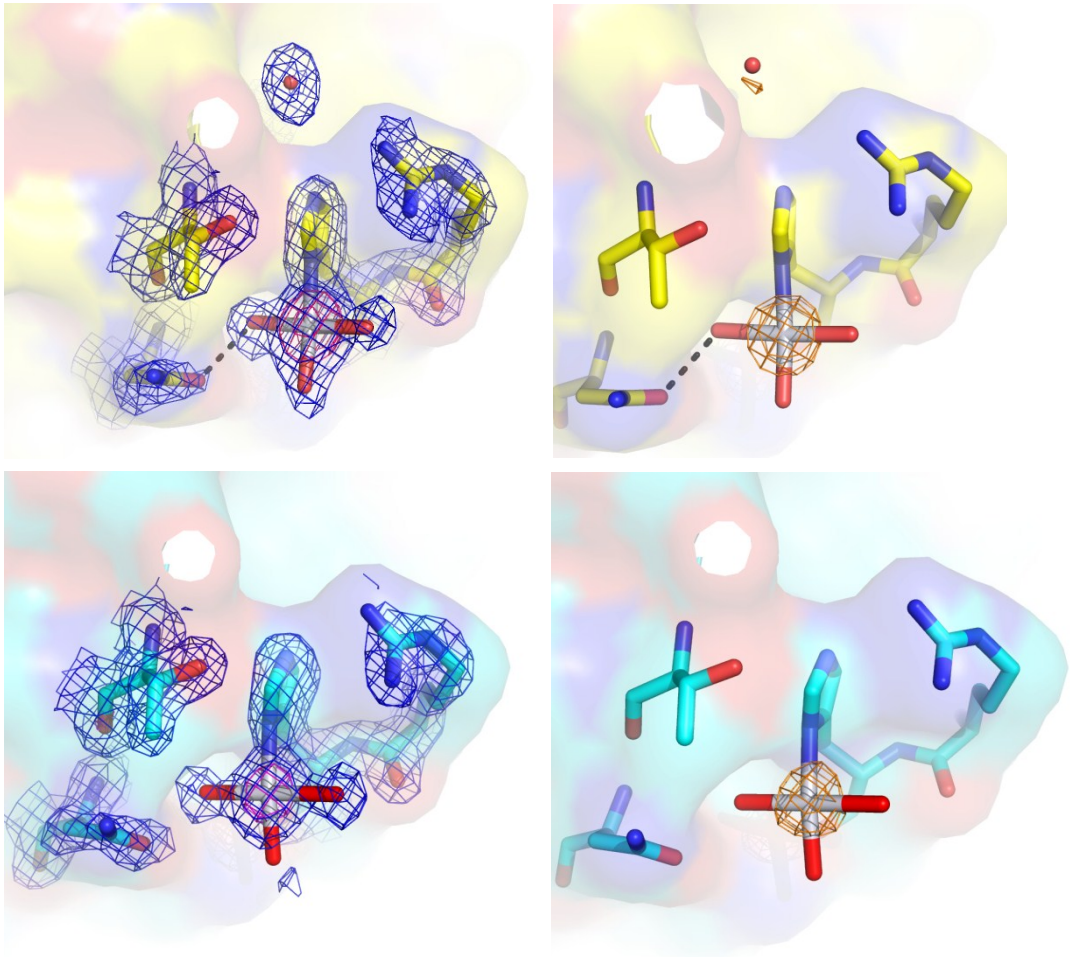


Figure S8. 2Fo – Fc electron density maps of the Pt binding sites in the HEWL-**Pt1** (panel A) and HEWL-**Pt2** (panel B) structures contoured at 1 σ (blue) and 4 σ (purple) obtained after model building and refinement. In panel C and D, anomalous electron density map of the Pt binding site in the two structures (contoured at 4.0 σ, gray) are also reported.

To verify the behavior of the compounds in the solution used to crystallize the adducts with HEWL, the absorption spectra of **Pt1**, in the absence and in the presence of HEWL, were registered in 1.1 M NaCl, 0.1 M sodium acetate pH 4.0 (Figure S9). In these solutions, the concentration of dmso is less than 1%. Under these experimental conditions, the compounds completely degrade: when spectra collected after 24 h were compared to those obtained at t = 0 h, significant changes were observed. In the presence of the protein (Figure S9), the degradation process is even more rapid.

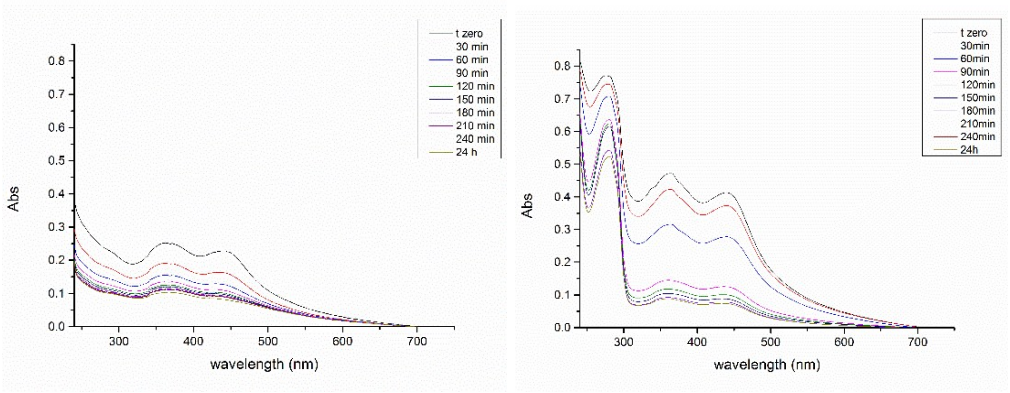


Figure S9. UV–visible time-course spectra of compound **Pt1** (0.6 mM) in the crystallization conditions in the absence (left) and in the presence of HEWL (right) over 4 h and upon 24 h. The Pt/HEWL ratio was 3:1

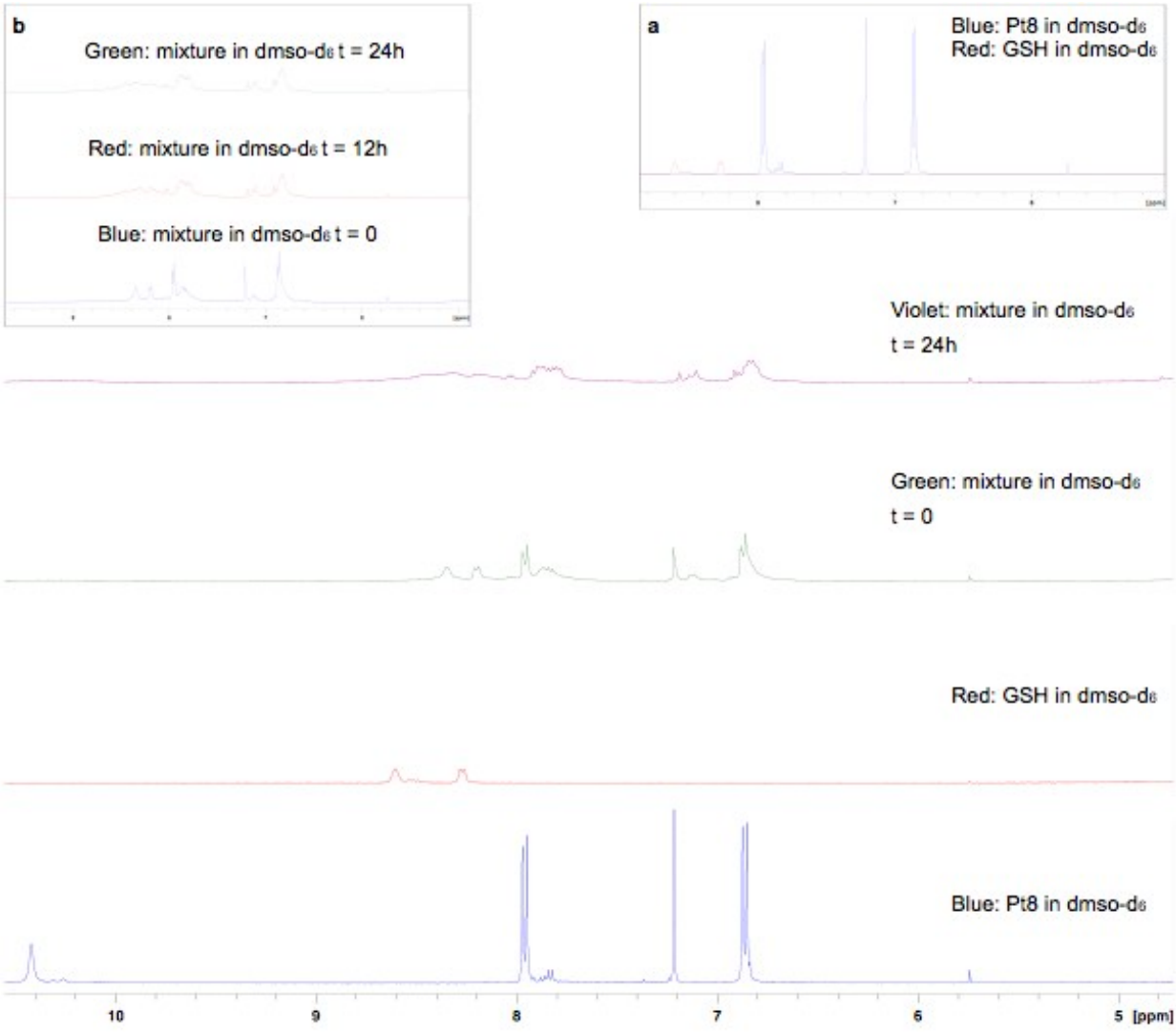


Figure S10. ^{1}H NMR spectroscopic investigation studying the interaction of Pt8 with glutathione

Table S1: Crystal data and refinement details for the X-ray structure determinations of the compounds **L1 - Pt3.**

Compound	**L1**	**L7**	**Pt1**	**Pt2**	**Pt3**
formula	$C_{11}H_{12}O_2S_2$	$C_{10}H_{10}O_2S_2$	$C_{13}H_{17}ClO_3PtS_3$	$C_{13}H_{17}ClO_3PtS_3$	$C_{13}H_{17}ClO_3PtS_3$
fw ($g \cdot mol^{-1}$)	240.33	226.30	547.99	547.99	547.99
°*C*	-140(2)	-140(2)	-140(2)	20(2)	-140(2)
crystal system	monoclinic	triclinic	monoclinic	trigonal	triclinic
space group	P 2_1/c'	P $\bar{1}$	P 2_1/c	P 3 c 1	P $\bar{1}$
a/ Å	10.4024(4)	3.9126(1)	10.9758(2)	34.3480(5)	7.2182(3)
b/ Å	14.0954(6)	11.6243(5)	19.2769(4)	34.3480(5)	10.6518(4)
c/ Å	7.7684(3)	22.2479(9)	8.0124(2)	7.2750(1)	22.3309(7)
α/°	90	98.186(2)	90	90	93.262(2)
β/°	92.530(2)	90.339(2)	96.398(1)	90	97.228(2)
γ/°	90	94.310(2)	90	120	100.948(2)
V/Å^3	1137.94(8)	998.58(6)	1684.70(6)	7433.04(18)	1666.54(11)
Z	4	4	4	18	4
ρ ($g \cdot cm^{-3}$)	1.403	1.505	2.161	2.204	2.184
μ (cm^{-1})	4.44	5.01	88.64	90.4	89.6
measured data	8017	6425	13229	64398	20804

data with I > 2σ(I)	2245	3245	3691	8758	6602
unique data (R_{int})	2583/0.0410	4098/0.0475	3830/0.0254	11219/0.0559	7539/0.0365
wR_2 (all data, on F^2)[a)]	0.1145	0.1506	0.0371	0.1397	0.0695
R_1 ($I > 2\sigma(I)$) [a)]	0.0493	0.0737	0.0162	0.0548	0.0296
S [b)]	1.166	1.169	1.098	1.064	1.041
Res. dens./e·Å^{-3}	0.467/-0.261	0.482/-0.432	0.548/-0.851	1.691/-1.083	1.127/-1.131
Flack-parameter	-	-	-	0.131(9)	-
absorpt method	multi-scan	multi-scan	multi-scan	multi-scan	multi-scan
absorpt corr $T_{min/max}$	0.6615/0.7456	0.6831/0.7456	0.5485/0.7456	0.0047/0.0206	0.6358/0.7456
CCDC No.	1446182	1446183	1446184	1446185	1446186

cont. Table S1: Crystal data and refinement details for the X-ray structure determinations of the compounds **Pt5 - Pt10.**

Compound	**Pt5**	**Pt6**	**Pt7**	**Pt9**	**Pt10**
formula	$C_{14}H_{19}ClO_3PtS_3$	$C_{14}H_{19}ClO_3PtS_3$	$C_{12}H_{15}ClO_3PtS_3$	$C_{13}H_{17}ClO_3PtS_3$	$C_{13}H_{17}ClO_3PtS_3$

fw ($g \cdot mol^{-1}$)	562.01	562.01	533.96	547.99	547.99
°C	-140(2)	-140(2)	-140(2)	-140(2)	-140(2)
crystal system	orthorhombic	monoclinic	monoclinic	monoclinic	monoclinic
space group	P b c n	C 2/c	P 2_1/c	P 2_1/c	P 2_1/c
a/ Å	18.6150(6)	22.8319(7)	12.8077(4)	12.8292(3)	5.6743(3)
b/ Å	7.3343(2)	7.1574(2)	16.5312(5)	17.2475(5)	10.8876(5)
c/ Å	27.2528(8)	43.9897(13)	7.3048(2)	7.3364(2)	28.1150(14)
α/°	90	90	90	90	90
β/°	90	96.662(1)	92.120(2)	92.953(2)	94.890(1)
γ/°	90	90	90	90	90
V/Å^3	3720.77(19)	7140.1(4)	1545.56(8)	1621.18(7)	1730.61(15)
Z	8	16	4	4	4
ρ ($g \cdot cm^{-3}$)	2.007	2.091	2.295	2.245	2.103
μ (cm^{-1})	80.29	83.68	96.58	92.11	86.29
measured data	21956	42371	3469	11189	9805
data with I > 2σ(I)	3588	7346	2718	3382	3257
unique data (R_{int})	4083/0.0728	8138/0.0457	3469/0.0211	3691/0.0385	3467/0.0401

wR_2 (all data, on F^2)[a)]	0.0825	0.0918	0.0512	0.0566	0.0690
R_1 ($I > 2\sigma(I)$) [a)]	0.0378	0.0426	0.0281	0.0248	0.0313
S [b)]	1.157	1.073	1.022	1.076	1.139
Res. dens./e·Å^{-3}	2.083/-1.628	1.192/-1.264	1.355/-1.039	0.874/-1.330	2.890/-1.026
absorpt method	multi-scan	multi-scan	multi-scan	multi-scan	'multi-scan'
absorpt corr $T_{min}/_{max}$	0.5777/0.7456	0.6226/0.7456	0.6128/0.7456	0.5549/0.7456	0.5413/0.7456
CCDC No.	1446187	1446188	1446189	1446190	1446191

[a)] Definition of the *R* indices: $R_1 = (\Sigma\square|F_o|-|F_c|\square)/\Sigma|F_o|$;
$wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ with $w^{-1} = \sigma^2(F_o^2) + (aP)^2+bP$; $P = [2F_c^2 + Max(F_O^2]/3$;
[b)] $s = \{\Sigma[w(F_o^2-F_c^2)^2]/(N_o-N_p)\}^{1/2}$.

Additional NMR Data

Table S2 shows the averages for these signals which are presented with respect to carbon side chain. It doesn't matter if aromatic-substitution is a hydroxy-group in case of compounds **7-10** or a methoxy-group in same position **2-6**. Compounds **11/12** just showing multipletts for their aromatic signals. For *para*-substituted compounds (**3/6,8/10**) there are two dubletts observed, because of symmetric substitution of these molecules. For *meta*-substituted molecules (**2/5, 7/9**) different signals are observed for protons in *ortho*-position. Compounds **1/4** which have an *ortho*-methoxy group show signals as proposed for these types of compounds with $^{4}J_{H\text{-}H}$ coupling.

Table S2. ^{1}H NMR spectroscopy data: Average chemical shifts for all aromatic proton signals. Platinum(II) complexes show same pattern as their corresponding ligands, also alkyl-substitution makes no differences so substance code is shown averages for all four substances.

^{1}H NMR Ar	**1/4**	**2/5**	**3/6**	**7/9**	**8/10**	**11/12**
ortho-postition	1. d (1H) δ~7.0 2. -OMe	1. m (1H) δ~7.5 2. m (1H) δ~7.5	d (2H) δ~6.9	1. s (1H) δ~7.4 2. d (1H) δ~7.4	d (2H) δ~6.8	m (2H) δ~7.5
meta-position	1. dd (1H) δ~7.8 2. ddd (1H) δ~7.0	1. t (1H) δ~7.3 2. -OCH_3	d (2H) δ~7.9	1. t (1H) δ~7.3 2. -OH	d (2H) δ~7.8	m (2H) δ~8.0
para-position	ddd (1H) δ~7.5	dd (1H) δ~7.1	-OCH_3	d/dd (1H) δ~7.0	-OH	m (1H) δ~7.5

Table S3. Data collection and refinement statistics.

Data collection	***Pt1***	***Pt2***	***Pt3***	***Pt4***
PDB code	5IHG	5ILC	5II3	5ILF
Space group	$P4_32_12$	$P4_32_12$	$P4_32_12$	$P4_32_12$
Unit cell parameter				
a=b (Å)	77.575	77.407	78.208	77.983
c (Å)	37.253	37.347	37.005	37.281
Observed reflections	71098	76725	79606	52253
Unique reflections	11472	11233	11254	10170
Resolution (Å)	54.85-1.75 (1.78-1.75)	54.74-1.75 (1.78-1.75)	55.30-1.78 (1.81-1.78)	55.14-1.85 (1.88-1.85)
Completeness (%)	95.3 (64.2)	93.7 (70.7)	97.6 (81.4)	98.6 (90.4)
Rmerge	0.058 (0.507)	0.040 (0.220)	0.052 (0.231)	0.042 (0.134)
I/σ(I)	44.1 (2.3)	7.6 (6.1)	49.1 (6.4)5	9.1 (5.1)
Multiplicity	6.2 (2.9)	6.8 (3.1)	7.1 (3.8)	5.1 (2.8)
Refinement				
Resolution (Å)	54.85-1.75	54.74-1.75	55.30-1.78	55.14-1.85
N. of reflections in working set	10868	10646	10677	9669
N. of reflections in test set	580	556	546	478
R factor (%)	16.1	15.8	15.3	16.6
Rfree (%)	20.3	21.1	19.0	23.3
Rall (%)	16.3	16.1	15.5	17.0
Number of non-H atoms	1176	1219	1172	1178

Mean B-value (Å)	29.9	25.6	21.3	24.2
Ramachandran values				
Most favoured (%)	97.4	91.3	97.6	95.0
Additional allowed (%)	2.6	8.7	2.4	5.0
Generously allowed (%)	0	0	0	0
Disallowed (%)	0	0	0	0
R.m.s.d. bonds (Å)	0.015	0.020	0.015	0.020
R.m.s.d. angles (°)	1.82	1.92	1.68	1.73

References

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