Supporting Information

General

All starting materials, reagents and solvents were purchased from Aldrich and used without further purification. All reactions were performed under an argon atmosphere unless otherwise stated. All chromatography columns that were eluted with chloroform/methanol were packed using chloroform, the sample was applied as a solution in chloroform and then eluted with chloroform/methanol. Compounds that showed poor solubility in chloroform were preadsorbed onto silica gel.

5-chloromethyluracil **6**[1]

A suspension of **5** (2.5 g, 17.6mmoles) in concentrated HCl (50 ml) was briefly warmed to 35°C and then stirred at room temperature for 15 minutes. The reaction mixture was frozen and then placed on a vacuum line equipped with an acid trap for 24 hours to give the product as a white solid (2.92 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.30 (s, 1H), 11.05 (bs, 1H), 7.75 (d, 1H, J=3), 4.40 (s, 2H).

2-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylmethyl)-2-methyl-malonic acid diethyl ester **7**

Diethylmethylmalonate (1.1ml, 9.3mmoles) and 150 mg of sodium hydride were added to 2 ml of dry THF. This viscous solution was stirred for 5 minutes and **6** (150 mg 0.93mmoles) was added. After 15 minutes, the reaction mixture was acidified with 10% HCl, extracted with chloroform (5x) and the extracts dried (Na_2SO_4). Unreacted diethylmethylmalonate was removed by vacuum distillation and the resulting solid was purified by chromatography (silica gel, 95:5 chloroform:methanol) to give **7** as a white solid (328 mg, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.2 (d, 1H, J=3), 9.90 (s, 1H), 7.33 (d, 1H, J=3), 4.16 (q, 4H, J=7.2), 2.93 (s, 2H), 1.40 (s, 3H), 1.21 (t, 6H, J=7.2). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 171.958, 165.054, 153.083, 140.893, 109.858, 61.792, 54.357, 31.387, 20.281, 14.196.

2-(1,3-Dimethyl-2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylmethyl)-2-methyl-malonic acid diethyl ester **8**

Sodium hydride (0.36 g, 15.0mmoles) followed by methyl iodide (0.97 ml, 19.6mmoles) was added to a solution of **7** (2.3 g, 6.9mmoles) in dry DMF (10ml). After 20 minutes, the reaction mixture was diluted with 40ml water, acidified with 10% hydrochloric acid, extracted with chloroform (3x) and the extracts dried (Na_2SO_4). The solvent was removed and the product was purified by chromatography (silica gel, 99:1 chloroform:methanol) to give **8** as a clear oil that solidified upon standing (2.43g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.215 (s, 1H), 4.171 (q, 4H, J=2.4), 3.373 (s, 3H), 3.325 (s, 3H), 2.947 (s, 2H), 1.407 (s, 3H), 1.24 (t, 6H, J=7.2). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 171.981, 164.083, 151.839, 142.735, 108.747, 61.658, 54.572, 37.192, 32.169, 28.300, 20.478, 14.212.

5-(1,3-Dimethyl-2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylmethyl)-5-methyl-pyrimidine-2,4,6-trione **9**

A solution of **8** (300 mg, 0.91mmoles) and methylurea (90 mg, 1.45mmoles) in 0.9 ml of 21 % ethanolic NaOEt was heated at reflux under argon for 7 hours.[2] The solvent was removed, the resulting dry residue was cooled in an ice bath and 0.4 ml of concentrated HCl and 2 ml of ice were added. The resulting crystallizing solution was placed in a

freezer for 15 hours. The product was filtered, washed with cold water and dried to give **9** as a white solid (174 mg, 70%). ^{1}H NMR (500 MHz, DMSO-d6) 11.30 (s,1H), 7.52 (s, 1H), 3.30 (s, 3H), 3.15 (s, 3H), 3.02 (s, 3H), 2.70 (s, 2H), 1.35 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 171.862, 171.793, 162.765, 151.013, 150.672, 143.586, 105.409, 50.716, 38.881, 37.295, 36.400, 27.524, 27.463, 19.891.

5-(1,3-Dimethyl-2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylmethyl)-1,3,5-trimethyl-pyrimidine-2,4,6-trione **10**

A suspension of **9** (560 mg, 1.83 mmoles) methyl iodide (0.14ml, 2.25mmoles) and K_2CO_3 (1.05 g, 7.7mmoles) in 4 ml dry DMF was stirred at room temperature for 24 hours. An additional 0.13 ml of methyl iodide was added and the reaction mixture was stirred for an additional 24 hours. The reaction mixture was then acidified with 10% HCl, diluted with water (20 ml), and extracted with chloroform (3x). The extracts were dried (Na_2SO_4) the solvent was removed and the product was purified by chromatography (silica gel, 99:1 chloroform:methanol) to give an oil which solidified upon standing. (0.53 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) 7.05 (s, 1H), 3.80 (s, 3H), 3.50 (s, 9H), 2.93 (s, 2H), 1.58 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 171.403, 163.080, 151.283, 151.086, 142.104, 107.024, 51.058, 38.070, 36.940, 28.655, 27.919, 23.041.

5-(4-Hydroxy-1,3,5-trimethyl-2,6-dioxo-hexahydro-pyrimidin-5-ylmethyl)-1,3-dimethyl-1*H*-pyrimidine-2,4-dione **11**

Sodium borohydride (20mg, 0.9mmoles) was added to a solution of **10** (160 mg, 0.5mmoles) in 10 ml dry methanol.[3] After stirring for 15 minutes, additional $NaBH_4$ (10 mg, 0.25mmoles) was added. After 5 minutes, 2 ml of saturated aqueous NH_4Cl was added, the solvent was removed, the product was extracted with chloroform (3x) and the extracts were dried (Na_2SO_4) and purified by chromatography (silica gel, 99:1 chloroform:methanol) to give **11** as a white solid (158 mg, 98%). Only one diastereomer of **11** is formed. ^{1}H NMR (500 MHz, $CDCl_3$) 7.208 (s,1H), 6.00 (bs, 1H), 4.219 (s, 1H), 3.451 (s, 3H), 3.380 (s, 3H), 3.194 (s, 3H), 3.085 (s, 3H), 3.024 (d, 1H, J=18.5), 2.776 (d, 1H, J=18.5), 1.24 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 173.837, 166.274, 153.164, 151.116, 144.652, 106.978, 84.446, 47.431, 37.506, 35.270, 30.164, 28.783, 28.123, 20.992.

1,3-Dimethyl-5-(1,3,5-trimethyl-2,4-dioxo-6-phenylsulfanyl-hexahydro-pyrimidin-5-ylmethyl)-1*H*-pyrimidine-2,4-dione **12**

Benzene thiol (25 µl, 0.24mmoles) followed by BF_3-etherate (38 µl, 0.32mmoles) was added to a solution of **11** (52 mg, 0.16 mmoles) in 1 ml of dry methylene chloride. After 15 minutes, 1 ml of saturated aqueous NH_4Cl was added, and the product was extracted with chloroform (3x), dried (Na_2SO_4) and concentrated. The resulting oil was purified by chromatography (silica gel, 99:1 chloroform:methanol) to give **12** as a clear oil which was a 1:1 mixture of diastereomers at C6 (58 mg, 88%).

^{1}H NMR diasteriomer A (500 MHz, $CDCl_3$) 7.72 (s, 1H), 7.35 (m,2H), 7.27 (m, 3H), 4.42 (s, 1H), 3.41 (s, 3H), 3.32 (s, 3H), 3.21 (d, 1H, J=19), 3.02 (s, 3H), 2.94 (d, 1H, J=19), 2.50 (s, 3H), 1.19 (s, 3H). ^{1}H NMR diasteriomer B (500 MHz, $CDCl_3$) 7.40 (m,2H), 7.32 (m, 3H), 6.79 (s, 1H), 4.60 (s, 1H), 3.35 (s, 6H), 3.07 (s, 3H), 2.75 (s, 3H), 2.67 (d, 1H, J=19), 2.60 (d, 1H, J=19), 1.24 (s, 3H). ^{13}C NMR both diasteriomers (400 MHz, $CDCl_3$) δ: 173.799, 172.039, 164.840, 163.740, 152.497, 152.413, 151.730, 151.412, 144.394, 141.549, 136.565, 136.178, 130.078, 129.760, 129.479, 129.418, 129.358, 108.639, 108.047, 74.196, 73.347, 48.296, 46.801, 37.273, 37.113, 36.469, 36.006, 35.604, 30.923, 28.419, 27.797, 27.683, 22.145, 21.622.

Radical induced cleavage of **12**

Bistributyltin (3.8 µl, 0.0075mmoles), tributyltin hydride (2.0 µl, 0.0075mmoles) and AIBN (0.25 mg in 0.25 ml of benzene, 0.0015mmoles) were added sequentially to a solution of **12** (6 mg, 0.015 mmoles) in 20 ml of dry benzene (0.75 mM).[4] The reaction mixture was heated under reflux for 2 hours, cooled and an additional 1 mg of AIBN and 4 µl of tributyltin hydride were added. The reaction mixture was heated at reflux for 1 hour, the solvent was removed and 2 ml of water were added. The product was extracted with chloroform (5x), dried and purified by chromatography (silica gel, 99:1 chloroform:methanol) to give the product as a white solid which was identical to a synthetic sample of **15** (4 mg, 85%). Only a trace of **13** was detected in the reaction mixture. ^{1}H NMR (500 MHz, $CDCl_3$) 7.00 (s,1H), 3.39 (s, 3H), 3.38 (s, 3H), 1.97 (s, 3H).

1,3-Dimethyl-5-(1,3,5-trimethyl-2,4-dioxo-hexahydro-pyrimidin-5-ylmethyl)-1*H*-pyrimidine-2,4-dione **13**

BF_3-etherate (5.0 µl, 0.32 mmoles) was added to a solution of **11** (6 mg, 0.16 mmoles) in 0.2 ml dry chloroform. After 5 minutes, $NaCNBH_3$ (6mg, 0.8mmoles) was added and the reaction mixture was diluted with 0.5ml THF. After 15 minutes, the solvent was removed and the crude reaction product was dissolved in 1 ml of water, extracted with chloroform (3x), dried (Na_2SO_4) and the solvent removed. The product was purified by chromatography (silica gel, 99:1 chloroform:methanol) to give a white solid (5 mg, 88%). ^{1}H NMR (500 MHz, CDCl3) 7.208 (s,1H), 3.323 (s, 3H), 3.306 (s, 3H), 3.280 (d, 1H, J=13.5), 3.14 (s, 3H) 3.02 (d, 1H, J=13.5), 2.98 (s, 3H), 2.760 (d, 1H, J=12.5), 2.620 (d, 1H, J=12.5), 1.23(s, 3H). ^{13}C NMR (400 MHz, CDCl3) d: 174.308, 164.400, 153.399, 151.563, 142.975, 108.305, 52.878, 43.668, 37.151, 36.142, 32.584, 28.305, 28.154, 22.820.

Attempted cysteine catalyzed cleavage of **13**

A solution of **13** (22 mg, 0.07 mmoles) and cysteine (87 mg, 0.7mmoles) in 0.12 ml of water adjusted to pH=9 with 6 M NaOH was stirred at room temperature under an argon atmosphere for 5 days. The reaction mixture was acidified with 10% hydrochloric acid, extracted with chloroform and analyzed by TLC (97:3 chloroform:methanol). No reaction occurred.

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