Supporting Information

Synthesis and SAR of Antitumor Pteridine Dione and Trione Monocarboxylate Transporter 1 Inhibitors

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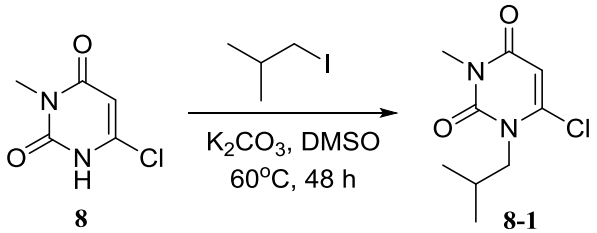
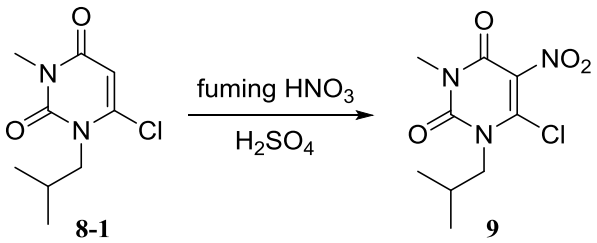
Experimental Section:

All reactions were performed in flame-dried glassware fitted with rubber septa under positive pressure of nitrogen or nitrogen, unless otherwise noted. Tetrahydrofuran, DMF, acetonitrile, and methylene chloride were purchased from Aldrich and used as received. Commercially available reagents were used without further purification. Thin layer chromatography (TLC) analyses were performed on pre-coated 250 μm silica 60 F254 glass-backed plates. Flash chromatography was performed on pre-packed columns of silica gel (230-400 mesh, 40-63 μm) by CombiFlash with EA/hexane or MeOH/DCM as eluents. Preparative HPLC was performed on a Shimadzu LC-8A preparative HPLC instrument on SunFire C_{18} OBD 10 μm (30 x 250 mm) with CH_3CN + 50% MeOH/H_2O + 0.1% TFA as eluents to purify the targeted compounds. LCMS was performed on Agilent Technologies 1200 series analytical HPLC instrument paired with a 6140 quadrupole mass spectrometer or with a Thermo Scientific UltiMate 3000 mass spectrometer. Analytical HPLC was performed on Agilent technologies 1200 series with CH_3CN (Solvent B)/H_2O + 0.9% CH_3CN + 0.1% TFA (solvent A) as eluents, and the targeted products were detected by UV in the detection range of 215-310 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker NMR spectrometer at 400 MHz (^1H) or 100 MHz (^{13}C). Unless otherwise specified, $CDCl_3$ was used as the NMR solvent. Resonances were reported in parts per million downfield from TMS standard, and were referenced to either the residual solvent peak (typically ^1H: $CHCl_3$ δ 7.27; ^{13}C: $CDCl_3$ δ 77.23). High resolution mass spectrometry was performed at the University of Illinois Urbana-Champaign Mass Spectrometry Laboratory.

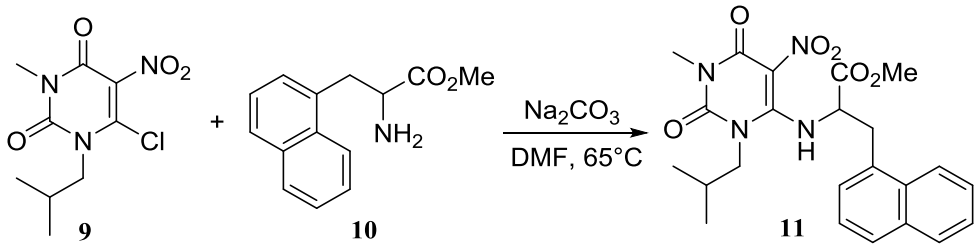


8 **8-1**

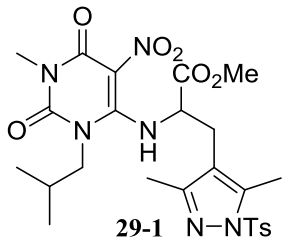
Synthesis of 6-Chloro-1-isobutyl-3-methylpyrimidine-2,4(1*H*,3*H*)-dione (8-1): K_2CO_3 (62.19 g, 450.0 mmol) was added to the suspension of **8** (40.14 g, 250.0 mmol) in DMSO (300 mL). The mixture was stirred at rt for 40 min, then 1-iodo-2-methylpropane (46.03 g, 250.0 mmol) was added and the resultant mixture was heated to 60 °C for 24 h. More 1-iodo-2-methylpropane (9.21 g, 50.0 mol) was added and stirred for an additional 24 h. Water was added to quench the reaction, extracted with EA. The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column (Hex:EA = 4:1) to afford 46.89 g (87%) of **8-1** as a colorless solid. R_f= 0.25 (hex:EA = 4:1); LC-MS (ESI): m/z 217 $[M+1]^+$; ^1H NMR δ (ppm) 0.96 (d, J=6.8 Hz, 6H), 2.16 (sep, *J*=6.9 Hz, 1H), 3.33 (s, 3H), 3.90 (d, *J*=7.0 Hz, 2H), 5.91 (s, 1H).



Synthesis of 6-Chloro-1-isobutyl-3-methyl-5-nitropyrimidine-2,4(1*H*,3*H*)-dione (9): H_2SO_4 (330 mL) was cooled to 0 ºC and added dropwise to **8-1** (46.89 g, 216.4 mmol) at 0 ºC. Fuming HNO_3 (26.4 g, 432.8 mmol) was added dropwise with vigorous stirring. The resultant mixture was stirred at 0 ºC for 3 h, then room temperature for 1 h. The reaction mixture was poured into ice and extracted with EA. The combined organic extracts were washed with H_2O, sat'd $NaHCO_3$, and brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column (hex:EA = 4:1) to afford 41.90 g (75%) of **9** as a yellow thick oil. R_f= 0.30 (hex:EA = 4:1); LC-MS (ESI): m/z 262 $[M+1]^+$; ^{1}H NMR δ (ppm) 1.01 (d, *J*=6.8 Hz, 6H), 2.19 (sep, *J*=6.8 Hz, 1H), 3.42 (s, 3H), 4.01 (d, *J*=7.6 Hz, 2H).

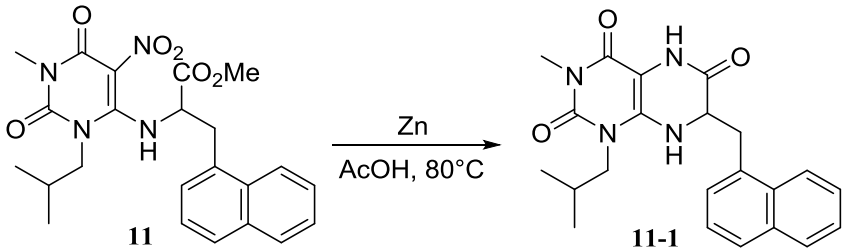


Synthesis of Methyl 2-((3-isobutyl-1-methyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)-3-(naphthaene-1-yl)propanoate (11): A mixture of **9** (1.44 g, 5.51 mmol), **10** (1.54 g, 5.78 mmol), Na_2CO_3 (1.46 g, 13.8 mmol) in DMF (11.0 mL) was heated to 65 ºC for 2 h. The reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl, extracted with EA. The combined organic extracts were washed with brine three times and dried over Na_2SO_4. The solvent was removed and the residue was purified by column (hex:EA = 3:2) to afford 1.69 g (67%) of **11** as a yellow oil. R_f= 0.50 (hex:EA = 1:1); LC-MS (ESI): m/z 455 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.36 (d, *J*=6.6 Hz, 3H), 0.44 (d, *J*=6.6 Hz, 3H), 1.55 (sep, *J*=6.6 Hz, 1H), 2.85-2.91 (m, 1H), 3.24 (s, 3H), 3.33-3.37 (m, 2H), 3.86 (s, 3H), 3.98-4.03 (m, 1H), 4.58-4.66 (m, 1H), 7.34 (d, *J*=6.8 Hz, 1H), 7.42-7.46 (m, 1H), 7.53-7.61 (m, 2H), 7.83 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=8.0 Hz, 1H), 8.02 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ (ppm) 19.0, 19.1, 26.8, 28.4, 36.1, 53.4, 53.6, 59.8, 116.5, 122.5, 125.5, 126.2, 126.9, 128.4, 128.7, 129.2, 130.8, 131.4, 133.9, 149.0, 154.9, 155.2, 170.6.



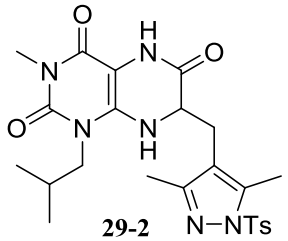
29-1

Methyl 3-(3,5-dimethyl-1-tosyl-1H-pyrazol-4-yl)-2-((3-isobutyl-1-methyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)propanoate (29-1): Follows the method for **11**. yellow solid. R_f= 0.15 (hex:EA = 1:1); LC-MS (ESI): m/z 577 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.73 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H), 1.93 (sep, *J*=6.8 Hz, 1H), 2.22 (s, 3H), 2.44 (s, 3H), 2.47 (s, 3H), 2.80-2.89 (m, 1H), 2.96-3.02 (m, 1H), 3.35 (s, 3H), 3.69 (s, 3H), 3.85-3.93 (m, 1H), 4.14 (d, *J*=7.6 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.87 (d, *J*=8.4 Hz, 2H).



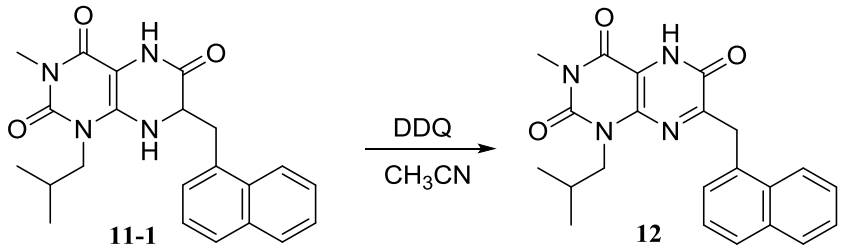
11 **11-1**

Synthesis of 1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-1,5,7,8-tetrahydropteridine-2,4,6(3*H*)-trione (11-1): A solution of **11** (3.57 g, 8.95 mmol) in AcOH (72 mL) was heated to 80 ºC under N_2. Zinc (7.02 g, 107.4 mmol) was added portionwise. The resultant mixture was stirred at 80 ºC for 1 h. The reaction was cooled to room temperature and filtered. The filtrate was concentrated. The residue was dissolved in EA, washed with H_2O, saturated $NaHCO_3$, and brine, dried over Na_2SO_4. The solvent was removed to afford 3.50 g (100%) of **11-1** as a yellow solid. R_f= 0.10 (hex:EA = 1:1); LC-MS (ESI): m/z 393 $[M+1]^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 0.58 (d, *J*=6.8 Hz, 3H), 0.70 (d, *J*=6.8 Hz, 3H), 1.56 (sep, *J*=6.8 Hz, 1H), 2.98-3.04 (m, 1H), 3.25-3.31 (m, 1H), 3.34 (s, 3H), 3.40-3.46 (m, 1H), 4.03-4.13 (m, 2H), 4.37-4.41 (m, 1H), 7.37 (d, *J*=6.4 Hz, 1H), 7.48-7.64 (m, 4H), 7.89 (d, *J*=8.0 Hz, 1H), 7.94-7.96 (m, 1H), 8.10-8.13 (m, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 19.5, 19.6, 27.5, 28.1, 35.1, 49.0, 56.5, 93.3, 123.1, 125.3, 126.2, 126.8, 127.9, 128.5, 129.1, 131.6, 131.8, 134.0, 138.4, 149.9, 155.5, 162.3.



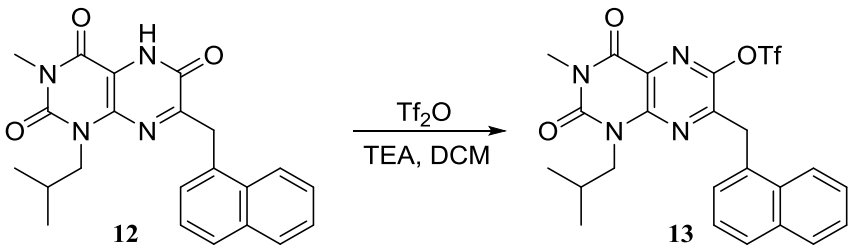
29-2

7-((3,5-dimethyl-1-tosyl-1*H*-pyrazol-4-yl)-1-isobutyl-3-methyl-1,5,7,8-tetrahydropteridine-2,4,6(3*H*)-trione (29-2): Follows the method for **11-1**. colorless oil. LC-MS (ESI): m/z 515 $[M+1]^+$.



11-1 **12**

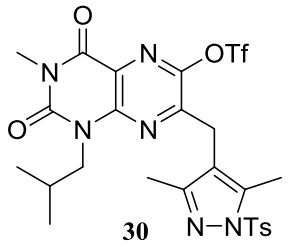
Synthesis of 1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-1,5-dihydropteridine-2,4,6(3*H*)-trione (12): A suspension of **11-1** (3.50 g, 8.95 mmol) in CH_3CN (90 mL) was treated with DDQ (2.09 g, 9.22 mmol) portionwise. The reaction mixture was stirred at room temperature for an additional 1 h. The precipitate was collected by filtration to afford 3.50 g (66%) of **12** as a yellow solid. LC-MS (ESI): m/z 391 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.15 (d, *J*=6.8 Hz, 6H), 1.27 (sep, *J*=6.8 Hz, 1H), 3.05 (s, 3H), 3.21 (d, *J*=7.2 Hz, 2H), 4.40 (s, 2H), 7.22-7.29 (m, 4H), 7.63 (dd, *J*=2.4, 6.8 Hz, 1H), 7.71 (d, *J*=8.4 Hz, 1H), 7.76 (d, *J*=8.0 Hz, 1H), 12.44 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 18.6, 25.8, 27.5, 35.2, 48.0, 116.1, 123.7, 124.6, 124.7, 125.2, 126.5, 127.3, 131.5, 132.8, 133.0, 138.5, 149.3, 153.4, 155.2, 157.9.



12 **13**

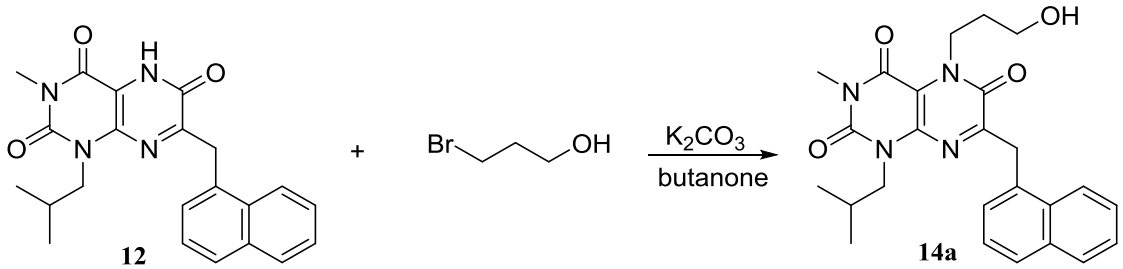
Synthesis of 1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropterdin-6-yl trifluoromethanesulfonate (13): A suspension of **12** (2.30 g, 5.88 mmol) in DCM (58 mL) was cooled to 0 ºC under N_2. Tf_2O (2.99 g, 10.6 mmol) was added followed by TEA (1.78 g, 17.6 mmol). The resultant mixture was stirred at 0 ºC for 1 h, quenched with saturated NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried over

Na_2SO_4. The solvent was removed and the residue was purified by column (Hex:EA = 4:1 to 2:1) to afford 3.01 g (98%) of **13** as a yellow solid. R_f= 0.25 (Hex:EA = 4:1); LC-MS (ESI): m/z 523 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.50 (d, *J*=6.8 Hz, 6H), 1.89 (sep, *J*=6.8 Hz, 1H), 3.47 (s, 3H), 3.65 (d, *J*=7.6 Hz, 2H), 4.80 (s, 2H), 7.47-7.52 (m, 4H), 7.85-7.93 (m, 3H); ^{19}F NMR δ (ppm) -71.8; ^{13}C NMR δ (ppm) 19.4, 26.6, 29.0, 36.3, 49.9, 117.0, 120.2, 122.3, 123.8, 125.5, 125.9, 126.5, 128.5, 129.0, 131.0, 132.0, 134.0, 146.1, 147.1, 150.2, 153.5, 158.2.



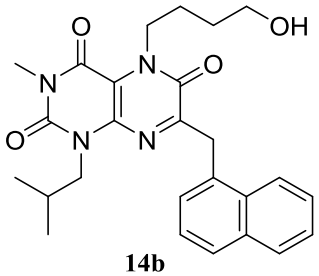
30

7-((3,5-dimethyl-1-tosyl-1H-pyrazol-4-yl)methyl)-1-isobutyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropteridin-6-yl trifluoromethanesulfonate (30): Follows the method for **13**. colorless oil. R_f= 0.10 (Hex:EA = 4:1); ^{1}H NMR δ (ppm) 0.78 (d, *J*=6.8 Hz, 6H), 1.94 (sep, *J*=6.8 Hz, 1H), 2.15 (s, 3H), 2.42 (s, 3H), 2.47 (s, 3H), 3.48 (s, 3H), 3.91 (d, *J*=7.6 Hz, 2H), 4.01 (s, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 7.84 (d, *J*=8.4 Hz, 2H).



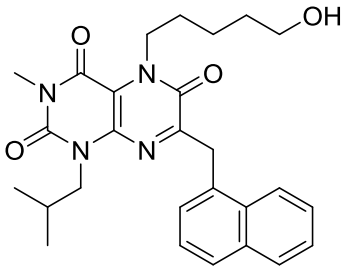
12 **14a**

Synthesis of 5-(3-hydropropyl)-1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-1,5-dihydropteridine-2,4,6(3*H*)-trione (14a) : A mixture of **12** (78 mg, 0.20 mmol), K_2CO_3 (83 mg, 0.60 mmol) in butanone (10 mL) was treated with 3-bromopropanol (56 mg, 0.40 mmol). The resultant mixture was refluxed for 14 h. The solvent was removed and the residue was dissolved in EA, washed with brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by preparative HPLC to afford 29 mg of **14a** as a yellow solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 449 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.56 (d, *J*=6.8 Hz, 6H), 1.71 (sep, *J*=6.8 Hz, 1H), 2.07-2.14 (m, 2H), 3.47 (s, 3H), 3.72 (d, *J*=6.8 Hz, 2H), 4.69 (s, 2H), 4.76-4.79 (m, 2H), 7.44-7.51 (m, 4H), 7.81-7.83 (m, 1H), 7.88-7.90 (m, 1H), 7.98-8.01 (m, 1H).



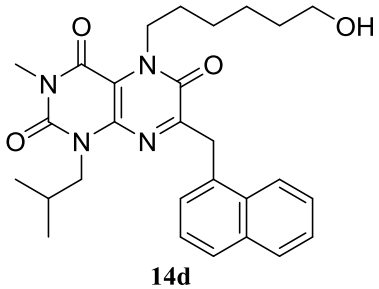
14b

5-(4-hydroxybutyl)-1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-1,5-dihydropteridine-2,4,6(3*H*)-trione (14b): Follows method for **14a**. White solid. >95% purity in analytical HPLC; LC-MS (ESI): m/z 463 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.56 (d, *J*=6.8 Hz, 6H), 1.69-1.76 (m, 4H), 1.99 (sep, *J*=6.8 Hz, 1H), 3.47 (s, 3H), 3.72 (d, *J*=7.6 Hz, 2H), 3.76-3.79 (m, 2H), 4.62 (t, *J*=6.8 Hz, 2H), 4.68 (s, 2H), 7.44-7.49 (m, 4H), 7.80-7.83 (m, 1H), 7.87-7.90 (m, 1H), 7.98-8.01 (m, 1H).



14c

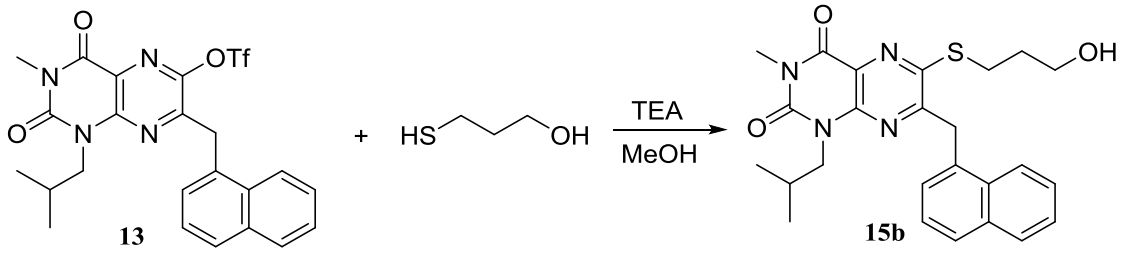
5-(5-hydroxypentyl)-1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-1,5-dihydropteridine-2,4,6(3*H*)-trione (14c): Follows method for **14a**. White solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 477 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.47 (d, *J*=6.8 Hz, 6H), 1.44-1.50 (m, 2H), 1.56-1.65 (m, 3H), 1.81-1.85 (m, 2H), 3.37 (s, 3H), 3.62-3.65 (m, 4H), 4.49 (s, 2H), 4.58 (s, 2H), 7.34-7.40 (m, 4H), 7.70-7.92 (m, 3H).



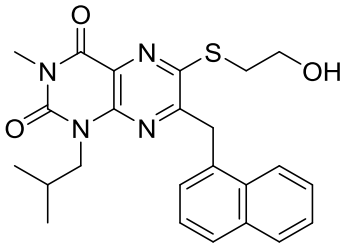
14d

5-(6-hydroxyhexyl)-1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-1,5-dihydropteridine-2,4,6(3*H*)-trione (14d): Follows method for **14a**. White solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 491

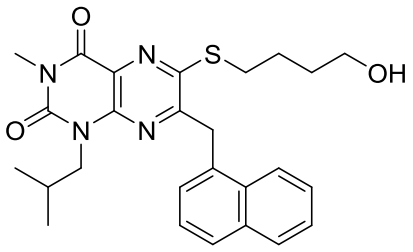
[M+1]$^+$; ^{1}H NMR δ (ppm) 0.47 (d, *J*=6.8 Hz, 6H), 1.39-1.44 (m, 4H), 1.52-1.63 (m, 3H), 1.80-1.85 (m, 2H), 3.37 (s, 3H), 3.60-3.65 (m, 4H), 4.49 (s, 2H), 4.58 (s, 2H), 7.34-7.40 (m, 4H), 7.70-7.92 (m, 3H).



Synthesis of 6-((3-hydroxypropyl)thio)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (15b): A solution of **13** (40 mg, 0.077 mmol) in MeOH (2 mL) was treated with 3-hydroxy-1-propanethiol (8.5 mg, 0.092 mmol) and Et_3N (16 mg, 0.15 mmol) under N_2. The resultant mixture was stirred at room temperature for 24 h. The reaction was concentrated and purified by column (Hex:EA = 3:2) to afford 6 mg of **15b** as a yellow solid. >95% purity in analytical HPLC; LC-MS (ESI): m/z 465 [M+1]$^+$; ^{1}H NMR δ (ppm) 0.40 (d, *J*=6.8 Hz, 6H), 1.47 (sep, *J*=7.0 Hz, 1H), 2.10 (d, *J*=5.4 Hz, 2H), 3.47 (s, 3H), 3.52 (d, *J*=7.6 Hz, 2H), 3.58 (t, *J*=6.2 Hz, 2H), 3.73-3.77 (m, 2H), 3.37 (t, *J*=7.0 Hz, 2H), 4.65 (s, 2H) 7.4-7.50 (m, 4H), 7.77 (d, *J*=8.0 Hz, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=8.0 Hz, 1H).

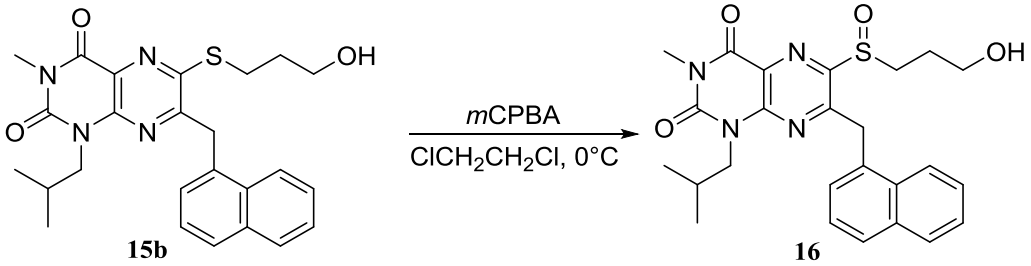


6-((2-hydroxyethyl)thio)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (15a): Follows method for **15b**. Yellow solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 451 [M+1]$^+$; ^{1}H NMR δ (ppm) 0.30 (d, *J*=6.8 Hz, 6H), 1.38 (sep, *J*=6.8 Hz, 1H), 3.37 (s, 3H), 3.41-3.48 (m, 4H), 3.98 (t, *J*=5.2 Hz, 2H), 4.56 (s, 2H) 7.29-7.41(m, 4H), 7.68-7.82 (m, 3H).



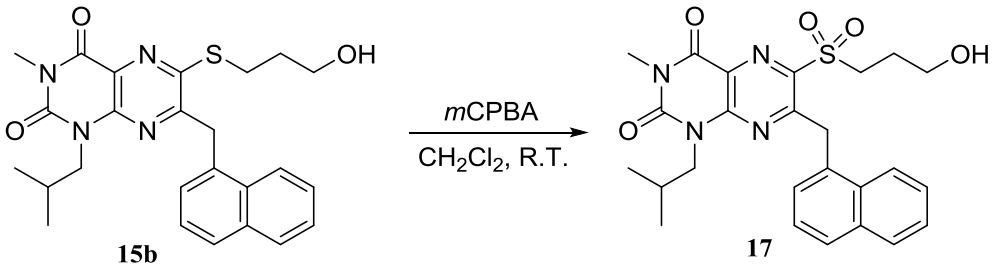
15c

6-((2-hydroxyethyl)thio)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (15c): Follows method for **15b**. Yellow solid. >95% purity in analytical HPLC; LC-MS (ESI): m/z 479 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.30 (d, *J*=6.8 Hz, 6H), 1.69 (sep, *J*=6.8 Hz, 1H), 1.88-1.98 (m, 4H), 3.30-3.36 (m, 2H), 3.39 (s, 3H), 3.42 (d, *J*=7.2 Hz, 2H), 3.80 (t, *J*=6.0 Hz, 2H), 4.53 (s, 2H), 7.32-7.40 (m, 4H), 7.64-7.75 (m, 3H).



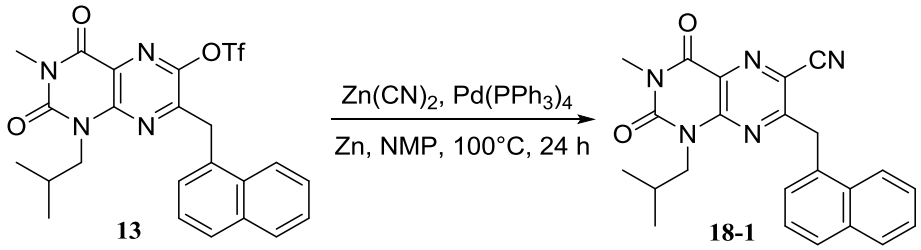
15b **16**

Synthesis of 6-((3-hydroxypropyl)sulfinyl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (16): A solution of **15b** (34 mg, 0.073 mmol) in $ClCH_2CH_2Cl$ (0.7 mL) was treated with *m*-CPBA (19 mg, 0.077 mmol) at 0 ºC. The resultant reaction was stirred at 0 ºC for 45 minutes. The reaction was quenched with saturated K_2CO_3, extracted with EA. The combined organic extracts were washed with brine, dried over Na_2SO_4. The reaction was concentrated and purified by preparative HPLC to afford 10 mg of **16** as a yellow solid. >95% purity in analytical HPLC; LC-MS (ESI): m/z 481 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.39 (dd, *J*=2.8, 6.4 Hz, 6H), 1.51 (sep, *J*=6.4 Hz, 1H), 2.05-2.06 (m, 2H), 3.30-3.49 (m, 5H), 3.56 (d, *J*=7.2 Hz, 2H), 3.71-3.73 (m, 2H), 4.93-5.04 (m, 2H), 7.32-7.40 (m, 4H), 7.73-7.84 (m, 3H).

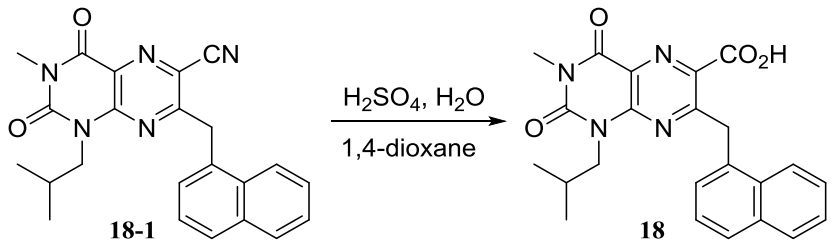


15b **17**

Synthesis of 6-((3-hydroxypropyl)sulfonyl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (17): A solution of **15b** (46 mg, 0.10 mmol) in CH_2Cl_2 (7 mL) was treated with *m*-CPBA (123 mg, 0.50 mmol) at room temperature. The resultant reaction was stirred for 12 h. The reaction was concentrated and the residue was purified by column (Hex:EA = 2:3) to afford 29 mg of **17** (58%) as a colorless oil. Single peak in analytical HPLC; LC-MS (ESI): m/z 497 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.05 (d, *J*=6.8 Hz, 6H), 1.06 (sep, *J*=6.8 Hz, 1H), 2.10-2.14 (m, 2H), 3.20 (d, *J*=7.6 Hz, 2H), 3.23 (s, 3H), 3.61 (s, 2H), 3.77-3.81 (m, 2H), 7.18-7.26 (m, 4H), 7.58-7.66 (m, 3H).

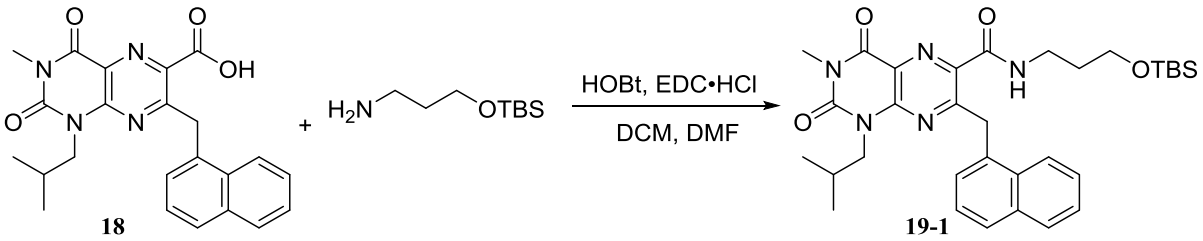


Synthesis of 1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carbonitrile (18-1): A mixture of **13** (314 mg, 0.60 mmol), $Zn(CN)_2$ (70 mg, 0.60 mmol), Zn (8.0 mg, 0.12 mmol) in NMP (6.0 mL) was degassed. $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) was added and the solution was again degassed. The resultant mixture was stirred at 100 ºC for 24 h, cooled to room temperature, quenched with saturated NH_4Cl, extracted with EA. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solution was concentrated and purified by flash column (Hex:EA = 3:1) to afford 151 mg (63%) of **18-1** as a yellow solid. LC-MS (ESI): m/z 400 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.55 (d, *J*=6.8 Hz, 6H), 1.66 (sep, *J*=6.8 Hz, 1H), 3.50 (s, 3H), 3.72 (d, *J*=7.6 Hz, 2H), 4.94 (s, 2H), 7.47-7.56 (m, 4H), 7.85-8.01 (m, 3H).



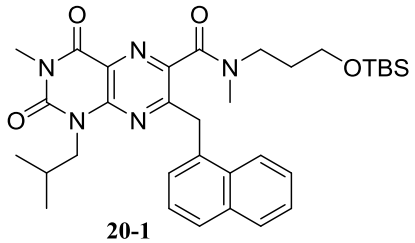
Synthesis of 1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (18): A solution of **18-1** (145 mg, 0.363 mmol) in 1,4-dioxane (18 mL) was treated with H_2SO_4 (11 mL, 60%). The resultant mixture was stirred at 110 ºC for 60 h, cooled to room temperature, diluted with H_2O, and extracted with EA. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solution was concentrated to afford 137 mg (90%) of **18** as a brown solid. LC-MS (ESI): m/z 419 $[M+1]^+$;

^{1}H NMR (DMSO-d_6) δ (ppm) 0.34 (d, *J*=6.8 Hz, 6H), 1.45 (sep, *J*=6.8 Hz, 1H), 3.26 (s, 3H), 3.41 (d, *J*=7.6 Hz, 2H), 3.41 (t, *J*=7.6 Hz, 2H), 5.05 (s, 2H), 7.41-7.52 (m, 4H), 7.86-7,98 (m, 3H).



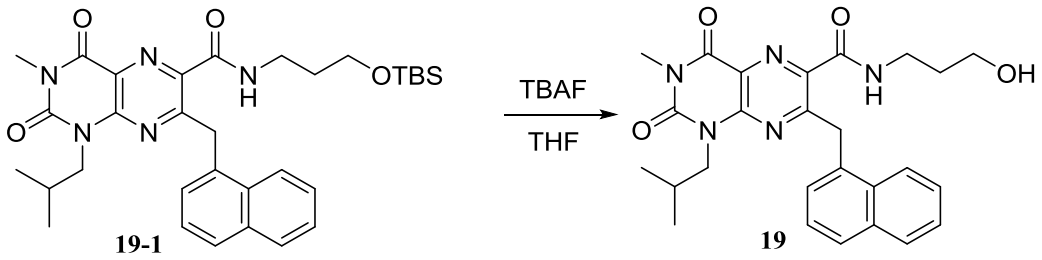
18 19-1

Synthesis of *N*-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxamide (19-1): A solution of **18** (34 mg, 0.082 mmol) in DMF (1.5 mL) and DCM (3.5 mL) was treated with EDC·HCl (28 mg, 0.15 mmol), HOBt (23 mg, 0.15 mmol), and 3-((t-butyldimethylsilyl)oxy)propan-1-amine (31 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 16 h, quenched with H_2O, extracted with EA. The combined organic extracts were washed with brine, dried over Na_2SO_4. The solution was concentrated and purified by flash column (Hex:EA = 2:1) to afford 39 mg (81%) of **19-1** as a colorless oil. R_f=0.60 (Hex:EA = 1:1); (LC-MS (ESI): m/z 590 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.00 (s, 6H), 0.27 (d, *J*=6.8 Hz, 6H), 0.82 (s, 9H), 1.36 (sep, *J*=6.8 Hz, 1H), 1.81-1.85 (m, 2H), 3.37 (s, 3H), 3.38 (d, *J*=7.6 Hz, 2H), 3.54 (t, *J*=6.8 Hz, 2H), 3.76 (t, *J*=6.0 Hz, 2H), 5.27 (s, 2H), 7.31-7.38 (m, 4H), 7.64-7.78 (m, 3H), 8.08 (s, 1H).



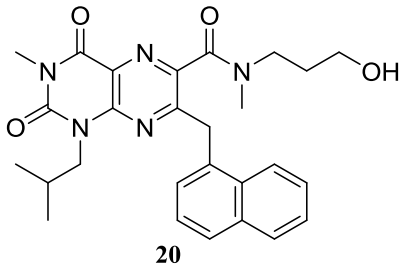
20-1

***N*-(3-((*tert*-butyldimethylsilyl)oxy-propyl)-1-isobutyl-*N*,3-dimethyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxamide (20-1)**: Follows method for **19-1**. Yellow oil. R_f=0.50 (Hex:EA = 1:1); (LC-MS (ESI): m/z 604 $[M+1]^+$.



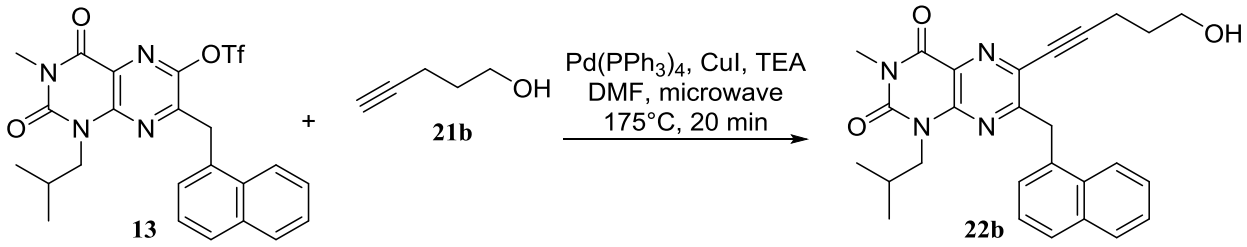
19-1 19

Synthesis of *N*-(3-hydroxypropyl)-1-isobutyl-3-methyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxamide (19): A solution of **19-1** (39 mg, 0.034 mmol) in THF (2.0 mL) was treated with TBAF (0.34 mL, 1.0 M in THF, 0.34 mmol). The reaction mixture was stirred at rt for 1 h, quenched with saturated NH_4Cl, extracted with EA. The combined organic extracts were washed with brine, dried over Na_2SO_4. The solution was concentrated and purified by flash column (Hex:EA = 1:9) and then by preparative HPLC to afford 18 mg of **19** as a white solid. R_f=0.20 (EA); Single peak in analytical HPLC; LC-MS (ESI): m/z 476 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.28 (d, *J*=6.4 Hz, 6H), 1.36 (sep, *J*=6.8 Hz, 1H), 1.82 (t, *J*=5.4 Hz, 2H), 3.38 (s, 3H), 3.40 (d, *J*=7.6 Hz, 2H), 3.61-3.70 (m, 4H), 5.28 (s, 2H), 7.29-7.38 (m, 4H), 7.70-7.79 (m, 3H), 8.51 (s, 1H).



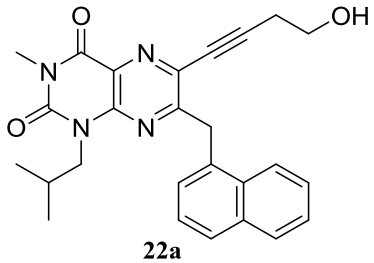
20

***N*-(3-hydroxypropyl)-1-isobutyl-*N*,3-dimethyl-7-(naphthalene-1-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxamide (20)**: Follows method for **19**. White solid. R_f=0.20 (EA); Single peak in analytical HPLC; LC-MS (ESI): m/z 490 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.28 (d, *J*=6.8 Hz, 6H), 1.53-1.57 (m, 2H), 1.95 (sep, *J*=6.8 Hz, 1H), 2.51 (t, *J*=6.2 Hz, 2H), 2.78 (s, 3H), 3.39 (s, 3H), 3.56-3.59 (m, 2H), 3.94 (d, *J*=7.6 Hz, 2H), 4.79 (s, 2H), 7.29-7.39 (m, 4H), 7.69-7.85 (m, 3H).



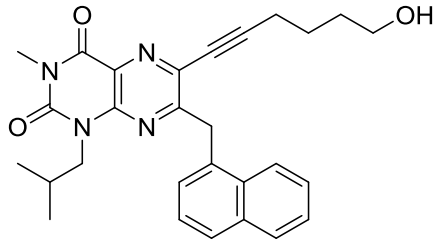
13 22b

Synthesis of 6-(5-(hydroxypent-1-yn-1-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (22b): A mixture of **13a** (261 mg, 0.50 mmol), **21b** (50 mg, 0.60 mmol), and CuI (9.5 mg, 0.05 mmol) in DMF (7.5 mL) was degassed. $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) was added followed by TEA (506 mg, 5.0 mmol). The resultant mixture was again degassed and heated by microwave to 175 ºC for 20 minutes. The reaction mixture was diluted with EA, washed with brine, dried over Na_2SO_4. The solution was concentrated and purified by flash column (Hex:EA = 2:3) to afford 105 mg (46%) of **22b** as a yellow solid. R_f = 0.10 (hexanes:EA = 1:1); LC-MS (ESI): m/z 457 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.39 (d, *J*=6.8 Hz, 6H), 1.52 (sep, *J*=6.8 Hz, 1H), 1.81-1.87 (m, 2H), 2.62 (t, *J*=7.0 Hz, 2H), 3.38 (s, 3H), 3.57 (d, *J*=7.6 Hz, 2H), 3.70-3.74 (m, 2H), 4.77 (s, 2H), 7.31-7.40 (m, 4H), 7.71-7.84 (m, 3H); ^{13}C NMR δ (ppm) 16.3, 19.4, 26.6, 29.0, 30.8, 39.0, 49.1, 61.3, 77.3, 98.4, 124.1, 124.5, 125.4, 125.7, 126.2, 127.9, 128.0, 128.8, 132.1, 133.2, 133.9, 134.6, 145.4, 150.4, 159.6, 161.8.



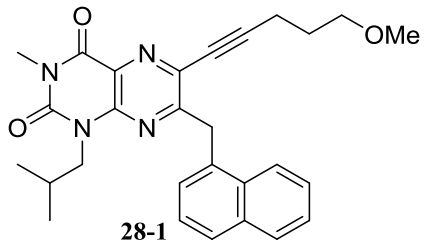
22a

6-(4-(hydroxybut-1-yn-1-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (22a): Follows method for **22b**. Yellow solid. LC-MS (ESI): m/z 443 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.35 (d, *J*=6.8 Hz, 6H), 1.46 (sep, *J*=6.8 Hz, 1H), 2.74 (t, *J*=6.2 Hz, 2H), 3.35 (s, 3H), 3.52 (d, *J*=7.6 Hz, 2H), 3.83 (t, *J*=6.2 Hz, 2H), 4.74 (s, 2H), 7.30-7.77 (m, 7H).



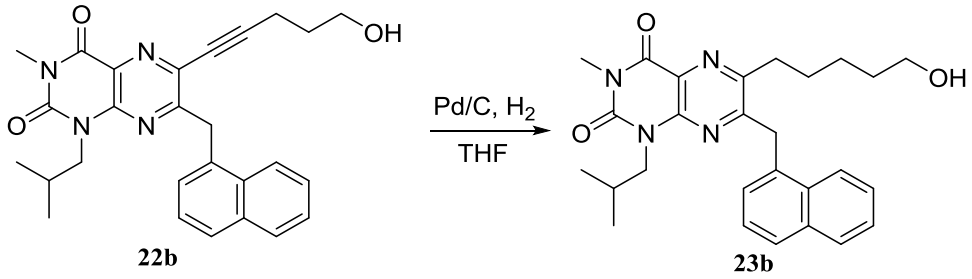
22c

6-(6-(hydroxyhex-1-yn-1-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (22c): Follows method for **22b**. Yellow solid. LC-MS (ESI): m/z 471 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.26 (d, *J*=6.8 Hz, 6H), 1.38 (sep, *J*=6.8 Hz, 1H), 1.50-1.60 (m, 4H), 2.38-2.42 (m, 2H), 3.26 (s, 3H), 3.43-3.48 (m, 4H), 4.64 (s, 2H), 7.17-7.61 (m, 7H).



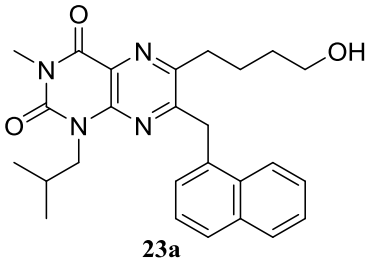
28-1

1-isobutyl-6-(5-methoxypent-1-yn-1-yl)-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (28-1): Follows method for **22b**. Yellow oil. LC-MS (ESI): m/z 471 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.46 (d, *J*=6.8 Hz, 6H), 1.58 (sep, *J*=6.8 Hz, 1H), 1.92-1.98 (m, 2H), 2.68 (t, *J*=7.2 Hz, 2H), 3.35 (s, 3H), 3.47 (s, 3H), 3.53 (t, *J*=6.0 Hz, 2H), 3.63 (d, *J*=7.6 Hz, 2H), 4.86 (s, 2H), 7.43-7.48 (m, 4H), 7.80-7.93 (m, 3H).



22b **23b**

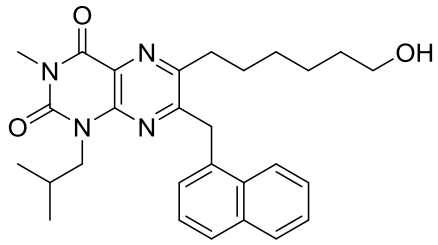
Synthesis of 6-(5-(hydroxypentyl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (23b): A solution of **22b** (20 mg, 0.044 mmol) in THF (2.0 mL) was treated with Pd/C (5.0 mg, 10%). The resultant mixture was stirred under H_2 for 5 h. The reaction was filtered, the filtrate was concentrated, and the residue was purified by column (Hex:EA = 2:3) and preparative HPLC to afford 10 mg of **23b** as a white solid. >97% purity in analytical HPLC; LC-MS (ESI): m/z 461 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.37 (d, *J*=6.8 Hz, 6H), 1.43-1.57 (m, 4H), 1.78-1.81 (m, 3H), 3.01 (t, *J*=7.4 Hz, 2H), 3.39 (s, 3H), 3.52 (d, *J*=7.6 Hz, 2H), 3.60-3.70 (m, 2H), 4.63 (s, 2H), 7.14 (d, *J*=6.8 Hz, 1H), 7.33-7.43 (m, 3H), 7.69-7.83 (m, 3H).



23a

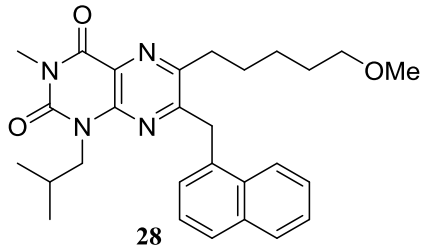
6-(4-(hydroxybutyl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (23a): Follows method for **23b**. White solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 447 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.37 (d, *J*=6.8 Hz, 6H), 1.49 (sep, *J*=6.8 Hz, 1H), 1.55-1.70 (m, 2H), 1.85-1.95 (m, 2H), 2.97-3.10 (m,

2H), 3.39 (s, 3H), 3.53 (d, *J*=7.6 Hz, 2H), 3.55-3.70 (m, 2H), 4.64 (s, 2H), 7.14 (d, *J*=6.8 Hz, 1H), 7.33-7.41 (m, 3H), 7.69-7.83 (m, 3H).



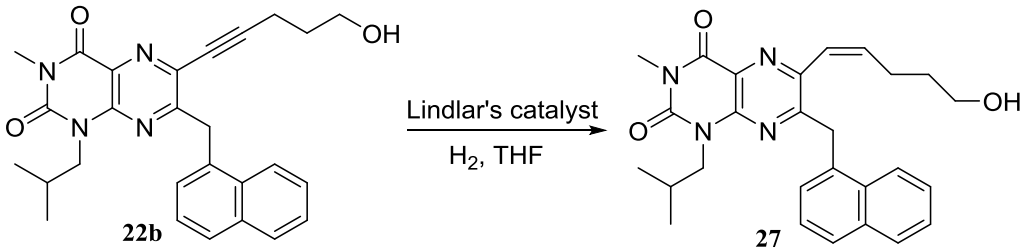
23c

6-(6-(hydroxyhexyl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (23c): Follows method for **23b**. White solid. >95% purity in analytical HPLC; LC-MS (ESI): m/z 475 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.47 (d, *J*=6.8 Hz, 6H), 1.40-1.50 (m, 4H), 1.57-1.62 (m, 3H), 1.82-1.92 (m, 2H), 3.11 (t, *J*=7.2 Hz, 2H), 3.50 (s, 3H), 3.62-3.67 (m, 4H), 4.73 (s, 2H), 7.24 (d, *J*=6.4 Hz, 1H), 7.43-7.53 (m, 3H), 7.80-7.93 (m, 3H).



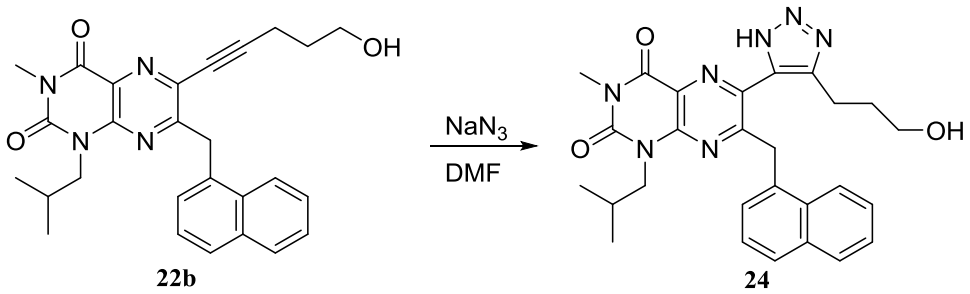
28

1-isobutyl-6-(5-methoxypentyl)-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (28): Follows method for **23b**. White solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 475 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.36 (d, *J*=6.8 Hz, 6H), 1.43-1.57 (m, 5H), 1.75-1.79 (m, 2H), 3.01 (t, J=8.0 Hz, 2H), 3.25 (s, 3H), 3.30 (t, J=6.4 Hz, 2H), 3.39 (s, 3H), 3.51 (d, *J*=7.6 Hz, 2H), 4.63 (s, 2H), 7.15 (d, *J*=6.4 Hz, 1H), 7.33-7.41 (m, 3H), 7.68-7.82 (m, 3H).



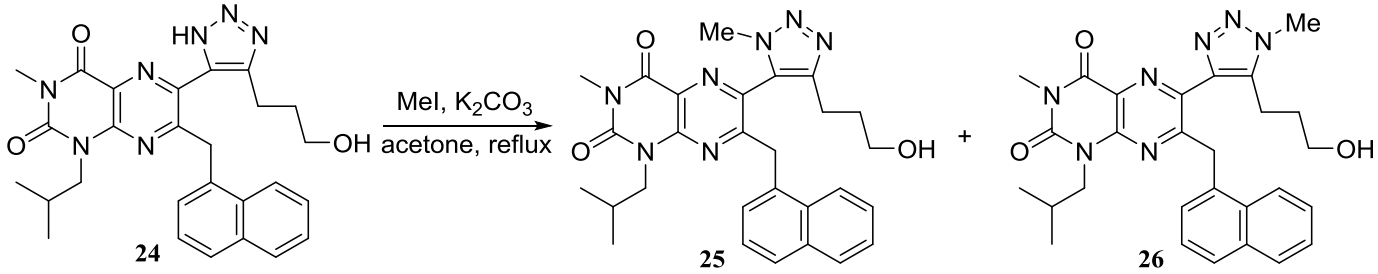
22b **27**

Synthesis of (*Z*)-6-(5-(hydroxypent-1-en-1-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (27): A solution of **22b** (24 mg, 0.053 mmol) in THF (2.0 mL) was treated with Lindlar's catalyst (8.0 mg, 5% on $CaCO_3$). The resultant mixture was stirred under H_2 for 1 h. The reaction was filtered and concentrated, and the residue was purified by preparative HPLC to afford 3 mg of **27** as a yellow solid. Single peak in analytical HPLC; LC-MS (ESI): m/z 459 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.37 (d, *J*=6.8 Hz, 6H), 1.49 (sep, *J*=6.8 Hz, 1H), 1.80-1.90 (m, 2H), 2.66 (q, *J*=6.8 Hz, 2H), 3.38 (s, 3H), 3.52 (d, *J*=7.6 Hz, 2H), 3.74 (t, J=5.0 Hz, 2H), 4.63 (s, 2H), 6.08 (d, J=11.6 Hz, 1H), 6.70 (d, J=11.6 Hz, 1H), 7.14 (d, *J*=6.8 Hz, 1H), 7.32-7.42 (m, 3H), 7.69-7.82 (m, 3H).



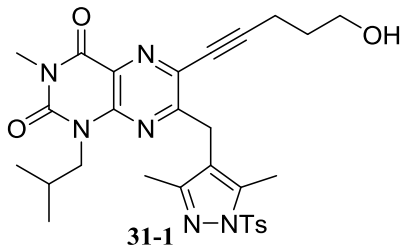
22b 24

Synthesis of 6-(4-(3-hydroxypropyl)-1*H*-1,2,3-triazol-5-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (24): A solution of **22b** (52 mg, 0.11 mmol) in DMF (2.0 mL) was treated with NaN_3 (9.0 mg, 0.14 mmol). The resultant mixture was stirred under N_2 at 100 ºC for 4 h. The reaction was cooled to room temperature, diluted with EA, washed with H_2O and brine, dried over Na_2SO_4. The reaction was concentrated and the residue was purified by column (Hex:EA = 1:4) and preparative HPLC to afford 5 mg of **24** as a white solid. R_f=0.25 (EA); Single peak in analytical HPLC; LC-MS (ESI): m/z 500 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.30 (d, *J*=6.8 Hz, 6H), 1.38 (sep, *J*=6.8 Hz, 1H), 2.01-2.11 (m, 2H), 3.13 (t, *J*=6.8 Hz, 2H), 3.39 (s, 3H), 3.44 (d, *J*=7.6 Hz, 2H), 3.71 (t, *J*=6.8 Hz, 2H), 5.11 (s, 2H), 7.20-7.37 (m, 4H), 7.65-7.79 (m, 3H).



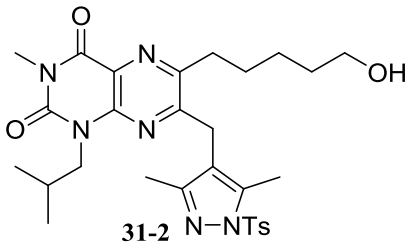
24 25 26

6-(4-(3-hydroxypropyl)-1-methyl-1*H*-1,2,3-triazol-5-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (25) and 6-(5-(3-hydroxypropyl)-1-methyl-1*H*-1,2,3-triazol-4-yl)-1-isobutyl-3-methyl-7-(naphthalen-1-ylmethyl)pteridine-2,4-(1*H*,3*H*)-dione (26): A solution of **24** (13 mg, 0.026 mmol) in acetone (10 mL) was treated with MeI (37 mg, 0.26 mmol) and K_2CO_3 (18 mg, 0.13 mmol). The resultant mixture was refluxed for 5 h. The reaction was concentrated. The residue was dissolved in EA, washed with brine, and dried over Na_2SO_4. The crude products were concentrated and the residue was purified by preparative HPLC to afford 4 mg of **25** as a yellow solid and 2 mg of **26** as a white solid. **25**: Single peak in analytical HPLC; LC-MS (ESI): m/z 514 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.29 (d, *J*=6.8 Hz, 6H), 1.37 (sep, *J*=6.8 Hz, 1H), 2.03-2.07 (m, 2H), 3.07 (t, *J*=7.2 Hz, 2H), 3.39 (s, 3H), 3.43 (d, *J*=7.6 Hz, 2H), 3.68 (t, *J*=5.2 Hz, 2H), 4.16 (s, 3H), 5.04 (s, 2H), 7.21 (d, *J*=6.8 Hz, 1H), 7.31-7.38 (m, 3H), 7.63-7.81 (m, 3H); **26**: Single peak in analytical HPLC; LC-MS (ESI): m/z 514 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.38 (d, *J*=6.8 Hz, 6H), 1.45 (sep, *J*=6.8 Hz, 1H), 2.09-2.14 (m, 2H), 3.22 (t, *J*=7.6 Hz, 2H), 3.49 (s, 3H), 3.52 (d, *J*=8.0 Hz, 2H), 3.85 (t, *J*=5.2 Hz, 2H), 4.17 (s, 3H), 5.34 (s, 2H), 7.35-7.48 (m, 4H), 7.75-7.89 (m, 3H).



31-1

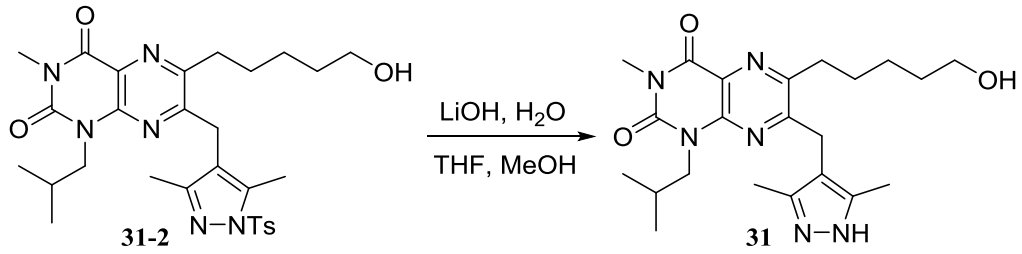
7-((3,5-dimethyl-1-tosyl-1-tosyl-1H-pyrazol-4-yl)methyl)-6-(5-hydroxypent-1-yn-1-yl)-1-isobutyl-3-methylpteridine-2,4-(1*H*,3*H*)-dione (31-1): Follows method for **22b**. Yellow oil. LC-MS (ESI): m/z 579 $[M+1]^+$.



31-2

7-((3,5-dimethyl-1-tosyl-1*H*-pyrazol-4-yl)methyl)-6-(5-hydroxypentyl)-isobutyl-3-methylpteridine-2,4(1*H*,3*H*)-dione (31-2): Follows method for **23b**. Yellow solid. LC-MS (ESI): m/z 583 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.64 (d, *J*=6.8 Hz, 6H), 1.42-1.55 (m, 4H), 1.74-1.84 (m, 3H), 2.00 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H),

2.85-2.95 (m, 2H), 3.41 (s, 3H), 3.55-3.65 (m, 2H), 3.73 (d, *J*=7.2 Hz, 2H), 3.83 (s, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 7.77 (d, *J*=8.4 Hz, 2H).



31-2 **31**

Synthesis of 7-((3,5-dimethyl-1*H*-pyrazol-4-yl)methyl)-6-(5-hydroxypentyl)-isobutyl-3-methylpteridine-2,4(1*H*,3*H*)-dione (31): A solution of **31-2** (16 mg, 0.027 mmol) in MeOH (1 mL) and THF (2 mL) was treated with a solution of LiOH (7 mg, 0.16 mmol) in H_2O (5 mL). The reaction was stirred at room temperature for 6 hours. The solution was quenched with TFA (80 μL). The solvent was removed and the residue was purified by preparative HPLC to afford 5 mg of **31** as a white solid. >95% purity in analytical HPLC; LC-MS (ESI): m/z 429 $[M+1]^+$; ^{1}H NMR δ (ppm) 0.66 (d, *J*=6.8 Hz, 6H), 1.44-1.55 (m, 4H), 1.75-1.84 (m, 3H), 2.17 (s, 3H), 2.18 (s, 3H), 2.95-3.00 (m, 2H), 3.35 (s, 3H), 3.49 (t, *J*=6.4 Hz, 2H), 3.78 (d, *J*=7.2 Hz, 2H), 4.15 (s, 2H).

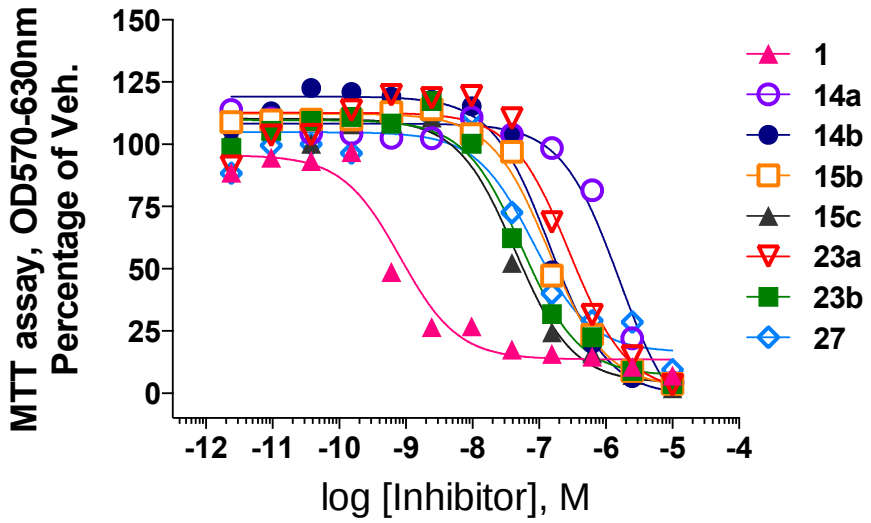
Biological Assay Methods:

Raji lymphoma cell MTT assay. Methods used were as previously described.[4] In brief, human Raji Burkitt lymphoma cells were seeded in 96-well plates at 20,000 cells/well and were cultured +/- compounds generated herein, or with vehicle, in 5% CO_2 incubator for 4 days. MTT reagents (Millipore CT0-A) were added at 10 μl per well and cells were incubated for 5 h. 100 μl Isoproponol/0.04N HCl was then added to each well, pipetted to mix, and plates were read using Biotek Synergy II plate reader at 570nm and 630nm. Experiments were performed in triplicate, and assays of the most active compounds were repeated three times. Representative data are shown in figures. EC_{50} values were determined using GraphPad Prism software.

MCF7_MCT1 ^{14}C-Lactate transport assay. Methods used were as previously described.[4] Briefly, MCF7 breast cancer cells engineered to overexpress MCT1 were cultured at 35,000 cell/well in 24-well plates for 2 days.[4] Assays were performed on ice by removing medium and washing once with cold buffer (150 mM NaCl, 10 mM Hepes, 5 mM KCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 0.2% BSA at pH 7.4) containing compound (1 nM – 1 μM) or DMSO for 5 minutes. Cells were incubated in 200 μl cold buffer containing 0.5 uCi/well L-14C(U)-Lactic acid, sodium salt (Perkin Elmer) and compounds for 10 min on ice. Cells were washed three times in cold buffer containing 0.1 mM Pholoretin (Sigma) and lysed with 200 μl 0.1 M NaOH for 30 min at room temperature. Radioactivity was measured by scintillation counting. Samples were done in triplicate and the log of compound concentration verses CPM incorporated was plotted using GraphPad Prism and used to calculate the IC_{50} for each compound.

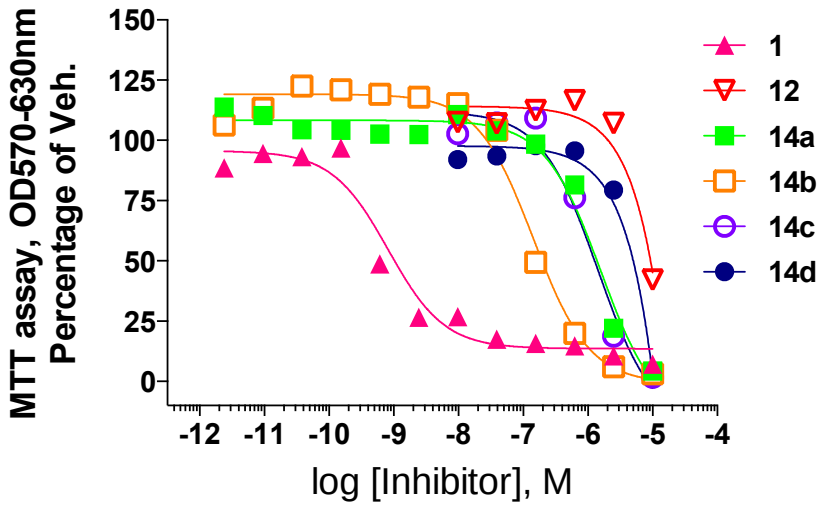
MCF7_MCT1 and MCF7_MCT4 MTT assays. MCF7_MCT1 and MCF7_MCT4 cells[4] were seeded in a 96 well plate at 2000/well. The following day, compounds were added and cultured for 4 days. All methods for culture and cell-handling followed the procedure that was described above for the Raji lymphoma-based MTT assays.

MTT Assay Data



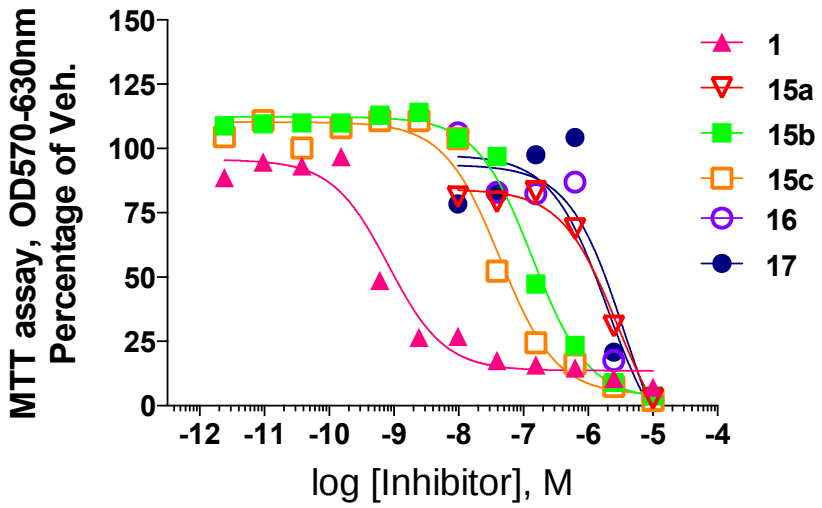
compound	EC_{50}
14a	1547 ± 192 nM
14b	150 ± 16 nM
15b	151 ± 32 nM
15c	37 ± 10 nM
23a	285 ± 41 nM
23b	58 ± 19 nM
27	70 ± 12 nM

The graph represents average data from three experiments for compounds **14b**, **15c**, **23a**, **23b**, and **27**.
The graph represents average data from four experiments for compounds **14a** and **15b**.
The percentage of inhibition is calculated by normalizing with the effect on null (DMSO-treated) cells.
EC_{50} values for all compounds are reported as Average ± S.E.M. in the table.



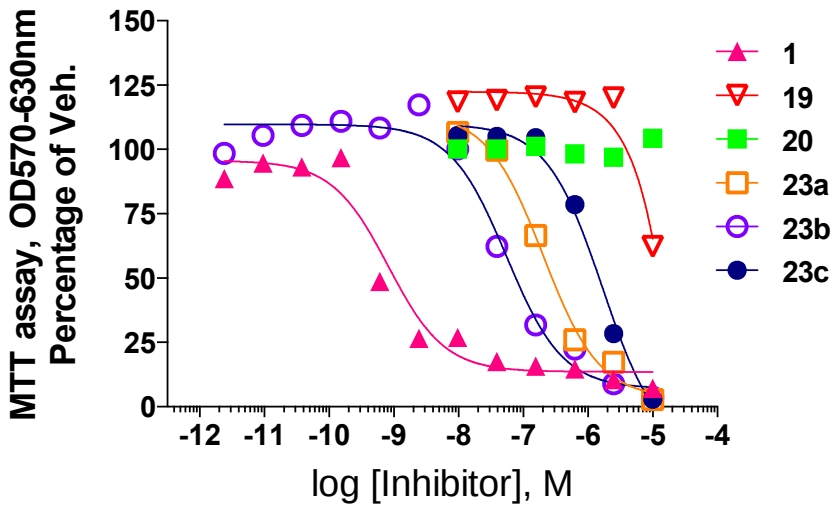
compound	EC_{50}
12	>10000 nM
14a	1547 ± 192 nM
14b	150 ± 16 nM
14c	1420 nM
14d	>10000 nM

The graph represents average data from four experiments for compound **14a.**
The graph represents average data from three experiments for compound **14b.**
The percentage of inhibition is calculated by normalizing with the effect on null (DMSO-treated) cells.
EC_{50} values for these compounds are reported as Average ± S.E.M. in the table.



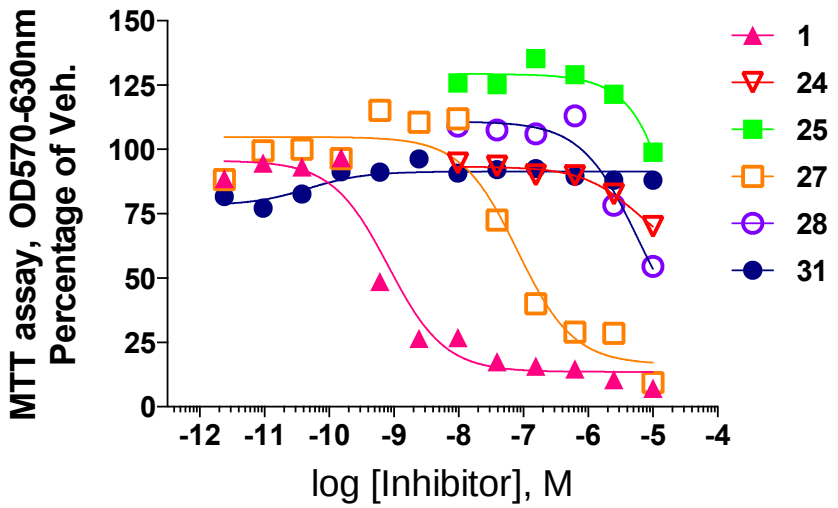
compound	EC_{50}
15a	2848 nM
15b	151 ± 32 nM
15c	37 ± 10 nM
16	1986 nM
17	3752 nM

The graph represents average data from four experiments for compound **15b.**
The graph represents average data from three experiments for compound **15c.**
The percentage of inhibition is calculated by normalizing with the effect on null (DMSO-treated) cells.
EC_{50} values for these compounds are reported as Average ± S.E.M. in the table.



compound	EC_{50}
19	>10000 nM
20	>10000 nM
23a	285 ± 41 nM
23b	58 ± 19 nM
23c	1687 nM

The graph represents average data from three experiments for compounds **23a** and **23b.**
The percentage of inhibition is calculated by normalizing with the effect on null (DMSO-treated) cells.
EC_{50} values for these compounds are reported as Average ± S.E.M. in the table.

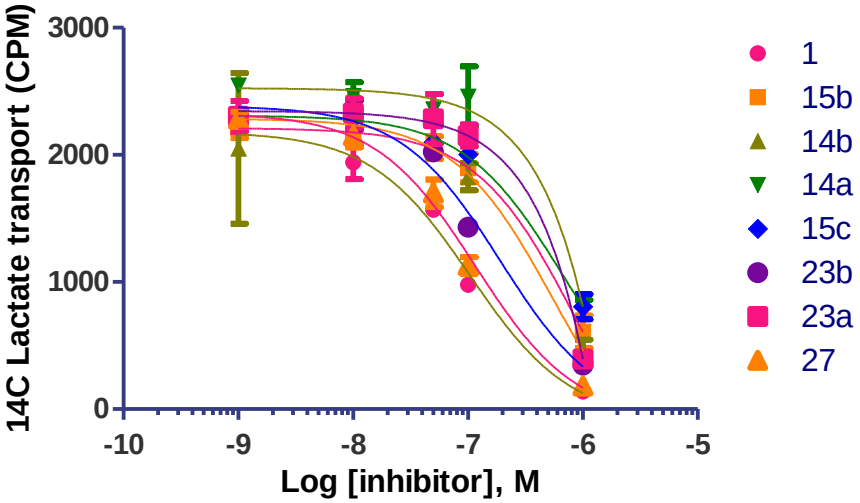


compound	EC_{50}
24	6016 nM
25	>10000 nM
27	70 ± 12 nM
28	5777 nM
31	>10000 nM

The graph represents average data from three experiments for compound **27.**
The percentage of inhibition is calculated by normalizing with the effect on null (DMSO-treated) cells.
EC_{50} values for this compounds is reported as Average ± S.E.M. in the table.

Lactate Transport Assay Data

	1	15b	14b	14a	15c	23b	23a	27
log(inhibitor) vs. response				Ambiguous			Ambiguous	
Best-fit values								
Bottom	-89.59	-767	-545.9	~-2.945e+006	-199.5	-58.93	~ -1.423e+006	-82.79
Top	2182	2211	2285	2525	2309	2386	2345	2329
LogIC50	-6.979	-6.067	-6.261	~ -2.766	-6.175	-6.717	~ -3.137	-6.934
IC50	1.049E-07	8.576E-07	5.482E-07	~ 0.001714	6.69E-07	1.918E-07	~ 0.0007300	1.164E-07
Span	2272	2978	2831	~ 2.948e+006	2509	2445	~ 1.426e+006	2412



Compound #	IC_{50} (nM)
1	104.9
14a	ambiguous
14b	548.2
15b	857.6
15c	669.0
23a	ambiguous
23b	191.8
27	116.4