Potent, selective small molecule inhibitors of type III phosphatidylinositol-4-kinase α- but not β- inhibit the phosphatidylinositol signaling cascade and cancer cell proliferation

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Supplementary information

Compound Synthesis

N-(5-(5-Amino-6-chloropyridin-3-yl)-4-methylthiazol-2-yl)acetamide

A suspension of N-(4-methylthiazol-2-yl)acetamide (1.2 g, 7.68 mmol), CsF (3.49 g, 23 mmol), 5-bromo-2-chloropyridin-3-amine (1.59 g, 7.68 mmol), palladium(II) acetate (90 mg, 0.4 mmol) and tri-tert-butylphosphine (162 mg, 0.8 mmol) in dimethylsulfoxide (20 mL) was degassed and purged with nitrogen then immediately heated at 150 °C for 40 minutes, cooled to room temperature and triturated with after (40 mL). The resulting brown solid was collected by filtration, washed with diethyl ether and dried in a vacuum oven at 40 °C for 3 days to afford N-(5-(5-amino-6-chloropyridin-3-yl)-4-methylthiazol-2-yl)acetamide (1.75 g, 80%). m.p. = 226.5-227 °C; MS (m/z) (ES+) [M+H]+ = 283.0; HRMS (m/z) [M]+ calcd. for C11H12ON4ClS, 283.04149; found, 283.04147; 1H NMR (400 MHz, DMSO-d6): δ 12.13 (s, 1H), 7.68 (d, J = 2.24 Hz, 1H), 7.22 (d, J = 2.24 Hz, 1H), 5.68 (s, 2H), 2.35 (s, 3H), 2.15 (s, 3H); 13C NMR (175 MHz, DMSO-d6): δ 30, 168.4, 155.6, 143.1, 141.2, 134.8, 133.6, 128.4, 120.8, 119.7, 22.3, 16.0

N-(5-(6-Chloro-5-(phenylsulfonamido)pyridin-3-yl)-4-methylthiazol-2-yl)acetamide

Benzenesulfonyl chloride (6.77 mL, 53.05 mmol) was added in one portion to N-(5-(5-amino-6-chloropyridin-3-yl)-4-methylthiazol-2-yl)acetamide (5 g, 17.68 mmol) in pyridine (95 mL) at 20 °C under nitrogen. The resulting solution was stirred at 45 °C for 20 hours. Water (80 mL) was added and the reaction mixture stirred for 30 minutes. Pyrrolidine (80 mL) was added and the reaction mixture stirred for 20 minutes. The reaction mixture was concentrated and diluted with water (300 mL) and acetic acid to bring the pH to 5. The organic was extracted with ethyl acetate (2 × 300 mL) and washed sequentially with water (300 mL) and saturated brine (150 mL). The organic layer was dried (MgSO4), filtered and evaporated to afford N-(5-(6-chloro-5-(phenylsulfonamido)pyridin-3-yl)-4-methylthiazol-2-yl)acetamide (2.97 g, 40 %) as a solid. m.p. = 210-210.5 °C; MS (m/z) (ES+) [M+H]+ = 283.0; HRMS (m/z) [M]+ calcd. for C17H15O3N4ClS2, 423.0349; found, 423.03473; 1H NMR (400 MHz, DMSO-d6): δ 10.45 (s, 1H), 8.31 (d, J = 2.29 Hz, 1H), 7.76 – 7.81 (m, 2H), 7.64 – 7.72 (m, 2H), 7.61 (m, 3H), 2.28 (s, 3H), 2.17 (s, 3H); 13C NMR (175 MHz, DMSO-d6): δ 168.6, 156.3, 145.0, 144.5, 143.4, 139.8, 133.7, 133.2, 130.6, 129.4, 128.4, 126.6, 118.4, 22.3, 15.8

N-(6-Bromopyridin-2-yl)benzenesulfonamide

Into a 500-mL round-bottom flask was placed a solution of 6-bromopyridin-2-amine (50 g, 289.00 mmol, 1.00 equiv) in pyridine (100 mL). This was followed by the addition of benzenesulfonyl chloride (61 g, 345.37 mmol, 1.20 equiv) dropwise with stirring at 0 °C in 30 min. The resulting solution was stirred for 2 h at room temperature and then diluted with 1 L of water, extracted with ethyl acetate (3 × 1 L). The organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was re-crystallized from ethyl acetate:hexane (1:3). This resulted in 78 g (86%) of N-(6-bromopyridin-2-yl)benzenesulfonamide as a solid. MS (m/z) (ES+) [M+H]+ = 313

N-(4-methyl-5-(6-(phenylsulfonamido)pyridin-2-yl)thiazol-2-yl)acetamide

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N-(6-bromopyridin-2-yl)benzenesulfonamide (1.0 g, 3.20 mmol), N-(4-methylthiazol-2-yl)acetamide (0.5 g, 3.20 mmol), diacetoxypalladium (0.057 g, 0.26 mmol), cesium fluoride (1.46 g, 9.60 mmol) and tri-tert-butylphosphine (1.24 mL, 0.51 mmol) in DMSO (6 mL) were stirred at 140 °C for 6 hours. After cooling, the mixture was poured into water (50 mL), and the solid was filtered off and dried. The resulting solid was diluted with dichloromethane/methanol mixture (50 mL) and the solid was absorbed onto silica gel and purified by flash chromatography on silica gel eluting with 50 to 100% ethyl acetate in heptane. Pure fractions were evaporated to dryness and filtered from a little diethyl ether to afford 35-(4-methyl-5-(6-benzenesulfonamidopyridin-2-yl)-4-methyl-1,3-thiazol-2-yl)piperidine-2-carboxamide (0.354 g, 90% yield) as a solid.  

MS (m/z) (ES+) [M+H]+ = 500

1-acetyl-N'-[5-(6-benzenesulfonamidopyridin-2-yl)-4-methyl-1,3-thiazol-2-yl]piperidine-2-carboxamide hydrochloride (3.2 g, 9.00 mmol) in hydrogen chloride (30 mL) was stirred for 40 h at 40 °C and then concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH3CN/water=0/100 increasing to CH3CN/water=60/40 within 30 min; Detector, UV 254 nm. This resulted in 1.7 g (59%) of 1-acetyl-N-[5-(6-benzenesulfonamidopyridin-2-yl)-4-methyl-1,3-thiazol-2-yl]piperidine-2-carboxamide as a solid.

**References**

1. C. The Royal Society of Chemistry [year]

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mobile phase, water with 0.05% trifluoroacetic acid and acetonitrile (5.0% acetonitrile up to 42.0% in 10 min, up to 95.0% in 2 min, down to 5.0% in 2 min); Detector, 220/254nm, affording 6-(6-ethoxyypyridin-3-yl)-1,3-benzothiazol-2-amine (110 mg, 64%) as a solid. 

8.44 (d, J = 2.33 Hz, 1H, 7.91 – 8.05 (m, 4H), 7.54 (dd, J = 1.86, 8.36 Hz, 1H), 7.42 (d, J = 8.36 Hz, 1H), 6.87 (d, J = 8.60 Hz, 1H), 4.35 (q, J = 7.03 Hz, 3H), 1.34 (t, J = 7.04 Hz, 3H). $^1$H NMR (175 MHz, DMSO-$d_6$): δ 167.81, 162.5, 158.0, 154.0, 150.4, 139.43, 131.9, 124.2, 119.2, 117.7, 113.7, 103.7, 36.2

5 6-(Pyridin-3-yl)benzo[d]thiazol-2-amine 5

1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (14.58 mg, 0.02 mmol) was added in one portion to tert-butyl (6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazol-2-yl)carbamate (150 mg, 0.40 mmol) and 3-bromopyridine (126 mg, 0.80 mmol) in degassed acetonitrile (3 mL) and 2M aq. potassium carbonate (1 mL) at 20 °C under nitrogen. The resulting mixture was further degassed and stirred in a microwave at 100 °C for 60 minutes. The mixture was well extracted with ethyl acetate. The mixture was concentrated. The residue was treated 20% TFA in dichloromethane (5 ml) and stirred at room temperature for 1.5 hours and concentrated in vacuo. The crude product was purified by preparative HPLC (Waters SunFire column, 5 μm silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% ammonia) and acetonitrile as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-(2-aminobenz[d]thiazol-6-yl)-1-methylpyridin-2(1H)-one (44.1 mg, 43.0 %) as a solid. 

15 4-(2-Aminobenz[d]thiazol-6-yl)-1-(cyclopentyl)methylpyridin-2(1H)-one 7

Into a 100-ml round-bottom flask purged with nitrogen, was placed a solution of N-(6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazol-2-yl)acetamide (636 mg, 2.00 mmol) in DME/water (20/5 mL), 4-bromo-1-(cyclopentyl)methyl-1,2-dihydropyridin-2-one (547 mg, 2.40 mmol, 1.20 equiv), Pd(dppf)Cl$_2$$_2$, 163 mg, 0.20 mmol, 0.10 equiv), sodium carbonate (636 mg, 6.00 mmol, 3.00 equiv). The resulting solution was stirred for 20 h at 100 °C. The resulting solution was diluted with 30 mL of water and extracted with ethyl acetate (3 x 30 mL). The organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (from 40:1 to 10:1). This resulted in 280 mg (47%) of 4-(2-aminobenz[d]thiazol-6-yl)-1-(cyclopentyl)methylpyridin-2(1H)-one as a solid.

4-(2-Aminobenz[d]thiazol-6-yl)-1-methylpyridin-2(1H)-one 6

1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (14.58 mg, 0.02 mmol) was added in one portion to tert-butyl (6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazol-2-yl)carbamate (150 mg, 0.40 mmol) and 4-bromo-1-methylpyridin-2(1H)-one (94 mg, 0.50 mmol) in degassed acetonitrile (3 mL) and 2M aq. potassium carbonate (1 mL) at 20 °C under nitrogen. The resulting mixture was further degassed and stirred within a microwave reactor at 100 °C for 60 minutes. The mixture was extracted with ethyl acetate. The mixture was concentrated and dissolved in dichloromethane / methanol mixture and was passed through a PL-Thiol MP SPE 500mg/6ml cartridge. The fractions containing product were concentrated in vacuo. The residue was treated 20% TFA in DCM (5 ml) and stirred at room temperature for 2.5 hours and concentrated in vacuo. The crude product was purified by preparative HPLC (Waters SunFire column, 5 μm silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 0.1% ammonia) and acetonitrile as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-(2-aminobenz[d]thiazol-6-yl)-1-methylpyridin-2(1H)-one (44.1 mg, 43.0 %) as a solid.
1 nM PI4KCA (Millipore, Dundee, UK), 72 µM ATP ($K_{\text{Mapp}}$ ATP) and 25 µM PI (K<sub>Mapp</sub> PI). The PI4Kβ assay was performed with 2 nM PI4KCB (SignalChem, UK), 220 µM ATP ($K_{\text{Mapp}}$ ATP) and 30 µM PI (<K<sub>Mapp</sub> PI). The assay was allowed to proceed for 45 min at ambient temperature before stopping the reaction by the addition of 5 µl of ADP-Glo reagent. Plates were then covered and incubated for 10 min at ambient temperature. 10 µl Kinase Detection Reagent was then added and plates were incubated for 30 min, before the luminescence signal was read with a PHERAstar plate reader (BMG Labtech GmbH, Offenburg, Germany).

**PIPK5γ ADP-Glo Assay**

The PIPK5γ assay was performed with the ADP-Glo™ Kinase Assay Kit (Promega, Madison, WI, USA) in Greiner 384-well white low volume plates. 20 nM PIK3CA (K<sub>Mapp</sub> PI) and PIP5K1C (expressed, purified and used at a 1:750 dilution, 4 nM total concentration). Assay incubations, additions and reads were performed as described for the PI4Ka and PI4Kβ ADP-Glo assays.

**PI3Kα ATP-Glo Assay**

The PI3Kα assay was performed using the Kinase-Glo® Plus Luminescence Assay Kit (Promega, Madison, WI, USA) in Greiner 384-well white low volume plates. 20 nM PIK3CA (expressed and purified by AZ) in phosphorylation buffer consisting of 50 mM Tris (pH 7.4), 0.05% CHAPSO, 10 mM MgCl<sub>2</sub> and 2.1 mM DTT was pre-incubated with or without an inhibitor at varying concentrations, 14 µM D-myo-Inositol 1,4,5-trisphosphate (Echelon Biosciences, Salt Lake City, UT, USA), 20 µM ATP ($K_{\text{Mapp}}$ ATP) and PIP5K1C (expressed, purified and used at a 1:750 dilution, 4 nM total concentration). Assay incubations, additions and reads were performed as described for the PI4Ka and PI4Kβ ADP-Glo assays.

**PI1 Cellular Assay**

The PI1 cell-based assay was performed using the HTRF IP-One Tbk kit (CisBio, Bedford, MA, USA) in Greiner 384-well TC-treated white low volume plates. NIH3T3 cells, stably transfected using SV40 with the PDGFRβ receptor, were cultured in DMEM, 10% Fetal Bovine Serum, 1% Glutamax and 1% Glutamin. After harvesting, cells were resuspended at a final concentration of 1.25 x 10<sup>6</sup> cells/ml in IP1 Cell Stimulation Buffer, and 8 µl was dispensed into each well of the assay plate pre-dosed with 55 nM PI4KCA (SignalChem, UK), 220 µM ATP ($K_{\text{Mapp}}$ ATP) and PIP5K1C (expressed, purified and used at a 1:750 dilution, 4 nM total concentration). Assay incubations, additions and reads were performed as described for the PI4Ka and PI4Kβ ADP-Glo assays.

**Lipid mass spectrometry analysis**

The Lipid extraction and derivitisation was carried out as per Clark J et al, Nature Methods 2011, B, 267.

Analysis of the derivatised lipids was performed on an API4000 mass spectrometer (ABSciex), connected to an Ultimate 3000 RS pump (Thermo Fisher Scientific) with 20ul of sample injected. The RS pump was connected to the API4000 flowing at 1-530, SRC, SRPK1, SRPK2, STE20, STK10, STK11, 105 ROCK2, ROS1, RPS6KA1, RPS6KA2, RPS6KA4, RPS6KA5, RAF1, RET V804L, RET V804M, RET, RIPK2, ROCK1, PRKCH, PRKCH, PRKG1, PTK2, PTK2b, PTK6, RAF1, RET V804L, RET V804M, RET, RIPK2, ROCK1, ROCK2, ROS1, RPS6KA1, RPS6KA2, RPS6KA4, RPS6KA5, RPS6KA6, RPS6KB1, SGK1, SGK2, SGK3, SIK1, SIK1, SRC, 1-530, SRC, SRPK1, SRPK2, STE20, STK10, STK11, STK17A, STK23, STK24, STK33, STK4, SYK, TA01, TA02, TA03, TBK1, TEC, TGFB1, TIE2, TLK2, TNK2, TSSK1B, TSSK2, TXK, TYK2, TYRO3, ULK2, ULK3, VRK2, WEE1, WNK2, WNK3, YES1, ZAP70, ZIPK.

The API4000 was set up with the Turbo Ion source working in
positive ion mode. The following settings were used: Curtain gas 10, GS1 30, GS2 50, TEM 1500C, ISV 4500V, Q1 resolution UNIT, Q2 resolution LOW, Collision Energy 40.

The following MRM method was used which consisted of transitions for the methylated species of PI, PIP, PIP2 and PIP3 (Internal standard and C18:0 20:4 species shown):

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</tr>
<tr>
<td>1165.6</td>
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<td>50.00</td>
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</tbody>
</table>

Mass spectrometry data of arachidonyl species of PI, PIP, PIP2 and PIP3 (C18:0 C20:4). Data plotted as Log PIx/total load area.

Compound 3 cell lines and pGI50s

SK-HEP-1, 6.1; Molm 13, 5.9; IM-9, 5.7; AMO-1, 5.7; JIN-3, 5.5; OCI-LY-19, 5.4; RS411, 5.4; Hep3B, 5.4; MV-4-11, 5.4; HCC1954, 5.2; OCI-AML2, 5.2; MDA-MB-231, 5.2; L-363, 5.2; SNU-5, 5.2; JVM-3, 5.2; MOLP-8, 5.2; KG-1, 5.0; ARH-77, 5.0; T47D, <5.0; SK-CO-1, <5.0; DMS 114, <5.0; PANCI-1, 5.7; NCI-H1703, 5.0; SNU-620, <5.0; SNU-878, <5.0; NCI-H126, <5.0; SNU-484, <5.0; SNU-1, <5.0; DU 145, <5.0; SW948, <5.0; CMK, <5.0; A2058, <5.0; Jurkat, <5.0; SNU-638, <5.0; HT-29, <5.0; HCC1419, <5.0; NCI-H1299, <5.0; LNCap-CasRes(AZ), <5.0; OE33, <5.0; BT-549, <5.0; 23132/87, <5.0; Calu-6, <5.0; COLO 320DM, <5.0; HICC1937, <5.0; HuH-7, <5.0; 22Rv1, <5.0; 647V, <5.0; 97-7, <5.0; A549, <5.0; BEL7404, <5.0; Calu-1, <5.0; Calu-3, <5.0; CAMA-1, <5.0; CC20, <5.0; COLO 205, <5.0; HARA, <5.0; HICA-7, <5.0; HCC1395, <5.0; HCC-15, <5.0; HCT 116, <5.0; HCT-15, <5.0; HCT-8, <5.0; HepG2, <5.0; HGC27, <5.0; HLE, <5.0; HLF, <5.0; HS746T, <5.0; HT1197, <5.0; HT1376, <5.0; IM95m, <5.0; J82, <5.0; Jeko-1, <5.0; K-562, <5.0; KU-19-19, <5.0; LK-2, <5.0; LCAP, <5.0; MCF7, <5.0; MCF7/madr+, <5.0; MDA-MB-453, <5.0; MEC-1, <5.0; MKI-6, <5.0; MKN74, <5.0; Molm 16, <5.0; MonoMac6, <5.0; NAMALWA, <5.0; NCI-H1437, <5.0; NCI-H1793, <5.0; NCI-H2085, <5.0; NCI-H2170, <5.0; NCI-H226, <5.0; NCI-H2291, <5.0; NCI-H358, <5.0; NCI-H460, <5.0; NCI-H460 DNp53, <5.0; NCI-H596, <5.0; NCI-H838, <5.0; Nono-1, <5.0; NUGC-3, <5.0; NUGC-4, <5.0; OCUM-1, <5.0; OE19, <5.0; PAM28, <5.0; PNT1A, <5.0; Raji, <5.0; Ramos, <5.0; Reh, <5.0; RERF-LC-AI, <5.0; RT112/84, <5.0; RT4, <5.0; SC-1, <5.0; ScabER, <5.0; SK-BR-3, <5.0; SMMC7721, <5.0; SNU-16, <5.0; SNU-216, <5.0; SNU-368, <5.0; SNU-739, <5.0; SNU-761, <5.0; SNU-886, <5.0; SUM52PE, <5.0; SW, <5.0; SW1710, <5.0; T24, <5.0; TCC-SUP, <5.0.

Compound 7 cell lines and pGI50s

SK-HEP-1, <5.0; Molm 13, 5.2; IM-9, 5.0; AMO-1, <5.0; JIN-3, <5.0; OCI-LY-19, <5.0; RS411, <5.0; Hep3B, 5.1; MV-4-11, 5.1; HCC1954, <5.0; OCI-AML2, <5.0; MDA-MB-231, 5.4; L-363, 5.4; SNU-5, <5.0; JVM-3, <5.0; MOLP-8, 5.3; KG-1, 5.2; ARH-77, <5.0; T47D, 5.8; SK-CO-1, 5.8; DMS 114, 5.7; PANCI-1, 5.7; NCI-H1703, 5.0; SNU-620, 5.6; SNU-878, 5.0; NCI-H126, 5.5; SW948, 5.5; JIMT-1, 5.5; NCI-H1869, 5.5; MDA-MB-468, 5.4; HICC1806, 5.4; RKO, 5.4; NCI-H2286, 5.4; LUDLU-1, 5.4; SNU-354, 5.4; NIH-OVCAR-3, 5.4; HCC1569, 5.4; GTL-16, 5.3; AZ21, 5.3; NCI-H23, 5.3; KATO III, 5.3; CCK-81, 5.3; MDA-MB-157, 5.3; He92.1.7, 5.3; MGH-U3, 5.3; SNU-668, 5.0; BEL7405, 5.5; RERF-LC-Sq1, 5.5; HICC1187, 5.2; C-99, <5.0; MHCC97L, <5.0; HCC95, <5.0; SNU-601, <5.0; RPMI-8226, <5.0; AGS, <5.0; BT-20, <5.0; NCI-H522, <5.0; SW480, <5.0; PC9, <5.0; SNU-449, <5.0; SK-MES-1, <5.0; HX147, <5.0; NCI-H322, <5.0; LS 180, <5.0; SW403, <5.0; HRA-19, <5.0; SW780, <5.0; SNU-398, <5.0; NCI-H647, <5.0; MIA PaCa-2, <5.0; LOVO, <5.0; BFTC-905, <5.0; SW620, <5.0; NCI-N87, <5.0; 1A6 [PTA-556], <5.0; NCI-H520, <5.0; MDA-MB-436, <5.0; HuH-7, <5.0; QGY7703, <5.0; HCC9810, <5.0; EBC-1, <5.0; NCI-H1216, <5.0; SNU-484, <5.0; SNU-1, <5.0; DU 145, <5.0; SW948, <5.0; CMK, <5.0; A2058, <5.0; Jurkat, <5.0; SNU-638, <5.0; HT-29, <5.0; HICC1419, 5.0; NCI-H1299, 5.0; LNCap-CasRes(AZ), 5.0; OEE3, 5.0; BT-549, 5.0;
23132/87, 5.0; Calu-6, 5.0; COLO 320DM, 5.0; HCC1937, 5.0; HuH-1, 5.0; 22Rv1, <5.0; 5637, <5.0; 647V, <5.0; 97-7, <5.0; A549, <5.0; BEL7404, <5.0; Calu-1, <5.0; Calu-3, <5.0; CAMA-1, <5.0; CC20, <5.0; COLO 205, <5.0; HARA, <5.0; HCA-7, <5.0; HCC1395, <5.0; HCC-15, <5.0; HCT 116, <5.0; HCT-15, <5.0; HCT-8, <5.0; HepG2, <5.0; HGC27, <5.0; HLE, <5.0; HLF, <5.0; HS746T, <5.0; HT1197, <5.0; HT1376, <5.0; IM95m, <5.0; J82, <5.0; JEKO-1, <5.0; K-562, <5.0; KU-19-19, <5.0; LK-2, <5.0; LNCaP, <5.0; MCF7, <5.0; MCF7/mdr+, <5.0; MDA-MB-453, <5.0; MEC-1, <5.0; MKN1, <5.0; MKN74, <5.0; Molm 16, <5.0; MonoMac6, <5.0; NAMALWA, <5.0; NCI-H1437, <5.0; NCI-H1793, <5.0; NCI-H1975, <5.0; NCI-H2085, <5.0; NCI-H2170, <5.0; NCI-H226, <5.0; NCI-H2291, <5.0; NCI-H358, <5.0; NCI-H460, <5.0; NCI-H460 Dnp53, <5.0; NCI-H596, <5.0; NCI-H838, <5.0; Nomo-1, <5.0; NUGC-3, <5.0; NUGC-4, <5.0; OCUM-1, <5.0; OE19, <5.0; PAMC82, <5.0; PNT1A, <5.0; Raji, <5.0; Ramos, <5.0; Reh, <5.0; RERF-LC-AI, <5.0; RT112/84, <5.0; RT4, <5.0; SC-1, <5.0; ScaBER, <5.0; SK-BR-3, <5.0; SMMC7721, <5.0; SNU-16, <5.0; SNU-216, <5.0; SNU-368, <5.0; SNU-739, <5.0; SNU-761, <5.0; SNU-886, <5.0; SUM52PE, <5.0; SW, <5.0; SW1710, <5.0; T24, <5.0; TCC-SUP, <5.0.