**Supplementary Materials**



**Figure S1.** Key of pathway analysis symbols.

**Table S2.** Enrichment analysis by GO processes

|  |  |  |  |
| --- | --- | --- | --- |
| **Processes** | **Network Objects from Active Data** | **Total** | ***p*-Value** |
| protein phosphorylation | PDGF-R-beta, PDGF receptor, ALS2CR7, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, GCK(MAP4K2), Ephrin-B receptors, Ephrin-B receptor 2, p38gamma (MAPK12), p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, JNK(MAPK8-10), JNK1(MAPK8), MAPK8/9, PFTAIRE-1, DDR1, PDGF-R-alpha, p38beta (MAPK11), MYO3B, Lck, Ephrin-A receptor 6, FAK1, ENO, ErbB2, LAT, **CDK3**, Insulin receptor, YES, PCTK2, ZAP70, CaMK II, CaMK II beta, ROS1, PCTK1, **CDK2**, CaMK II gamma, JNK3(MAPK10), Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JNK2(MAPK9), JAK2, c-Src, STK36, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), FRK, ITK, MER, FGFR2, CaMK II alpha, **CDK1** (p34), BCKD-kinase, c-Fes, CALM3, CALM2, Calmodulin, ERK5 (MAPK7), STK4, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, c-Cbl, TrkC, ROR1, ULK3, unc-51-like kinase 3 (C. elegans), FGFR1, IRR, VEGFR-2, p38delta (MAPK13), Ephrin-A receptor 1, Ephrin-B receptor 1, MYO3A, Myosin IIIA, Myosin IIIA, GLK(MAP4K3), DCAMKL1, Ephrin-A receptor 2, PCTK3, LTK, Pyk2(FAK2), STK3, IGF-1 receptor, EGFR, ErbB4, p120GAP, RET, MSP receptor (RON), **CDK5**, TrkA, FGFR3, Myelin basic protein, Hck, HGF receptor (Met), TEC, ENO1, VEGFR-3, Fer, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, c-Raf-1, Ephrin-A receptor 4, STAT4 | 1291 | 1.313 × 10−91 |
| phosphorylation | PDGF-R-beta, PDGF receptor, ALS2CR7, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, BCKD, GCK(MAP4K2), Ephrin-B receptors, Ephrin-B receptor 2, p38gamma (MAPK12), p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, JNK(MAPK8-10), JNK1(MAPK8), MAPK8/9, PFTAIRE-1, DDR1, PDGF-R-alpha, p38beta (MAPK11), MYO3B, Lck, Ephrin-A receptor 6, FAK1, ENO3, ENO, ErbB2, LAT, **CDK3**, Insulin receptor, YES, PCTK2, ZAP70, CaMK II, CaMK II beta, ROS1, PCTK1, **CDK2**, CaMK II gamma, JNK3(MAPK10), Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JNK2(MAPK9), JAK2, c-Src, STK36, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), FRK, ITK, MER, FGFR2, CaMK II alpha, **CDK1** (p34), BCKD-kinase, c-Fes, CALM3, CALM2, Calmodulin, ERK5 (MAPK7), ESR1 (nuclear), ESR1 (mitochondrial), ESR, ESR1 (membrane), STK4, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, c-Cbl, TrkC, ROR1, ULK3, unc-51-like kinase 3 (C. elegans), FGFR1, IRR, VEGFR-2, p38delta (MAPK13), Ephrin-A receptor 1, Ephrin-B receptor 1, MYO3A, Myosin IIIA, Myosin IIIA, GLK(MAP4K3), DCAMKL1, Ephrin-A receptor 2, PCTK3, LTK, Pyk2(FAK2), STK3, IGF-1 receptor, EGFR, ENO2, ErbB4, p120GAP, RET, MSP receptor (RON), **CDK5**, TrkA, FGFR3, Myelin basic protein, Hck, HGF receptor (Met), TEC, ENO1, VEGFR-3, Fer, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, c-Raf-1, Ephrin-A receptor 4, STAT4 | 1691 | 3.775 × 10−87 |
| peptidyl-tyrosine phosphorylation | PDGF-R-beta, PDGF receptor, Ephrin-A receptor 3, Ephrin-A receptors, Ephrin-B receptors, Ephrin-B receptor 2, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, DDR1, PDGF-R-alpha, Lck, Ephrin-A receptor 6, FAK1, ErbB2, Insulin receptor, YES, ZAP70, ROS1, Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JAK2, c-Src, FRK, ITK, MER, FGFR2, c-Fes, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, TrkC, ROR1, FGFR1, IRR, VEGFR-2, Ephrin-A receptor 1, Ephrin-B receptor 1, Ephrin-A receptor 2, LTK, Pyk2(FAK2), IGF-1 receptor, EGFR, ErbB4, RET, MSP receptor (RON), TrkA, FGFR3, Hck, HGF receptor (Met), TEC, VEGFR-3, Fer, ALK, Ephrin-B receptor 4, TrkB, Ephrin-A receptor 4 | 226 | 1.345 × 10−80 |
| peptidyl-tyrosine modification | PDGF-R-beta, PDGF receptor, Ephrin-A receptor 3, Ephrin-A receptors, Ephrin-B receptors, Ephrin-B receptor 2, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, DDR1, PDGF-R-alpha, Lck, Ephrin-A receptor 6, FAK1, ErbB2, Insulin receptor, YES, ZAP70, ROS1, Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JAK2, c-Src, FRK, ITK, MER, FGFR2, c-Fes, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, TrkC, ROR1, FGFR1, IRR, VEGFR-2, Ephrin-A receptor 1, Ephrin-B receptor 1, Ephrin-A receptor 2, LTK, Pyk2(FAK2), IGF-1 receptor, EGFR, ErbB4, RET, MSP receptor (RON), TrkA, FGFR3, Hck, HGF receptor (Met), TEC, VEGFR-3, Fer, ALK, Ephrin-B receptor 4, TrkB, Ephrin-A receptor 4 | 229 | 3.549 × 10−80 |
| protein auto-phosphorylation | PDGF-R-beta, PDGF receptor, PDK (PDPK1), Ephrin-A receptors, Ephrin-B receptors, p38 MAPK, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, DDR1, PDGF-R-alpha, MYO3B, Lck, FAK1, ErbB2, Insulin receptor, YES, ZAP70, CaMK II, CaMK II beta, ROS1, CaMK II gamma, JAK1, DDR2, Syk, JAK2, c-Src, FRK, ITK, FGFR2, CaMK II alpha, c-Fes, ERK5 (MAPK7), STK4, Tyro3, Ephrin-B receptor 3, TrkC, ULK3, unc-51-like kinase 3 (C. elegans), FGFR1, IRR, VEGFR-2, Ephrin-A receptor 1, Ephrin-B receptor 1, MYO3A, Myosin IIIA, Myosin IIIA, Pyk2(FAK2), IGF-1 receptor, EGFR, ErbB4, **CDK5**, TrkA, FGFR3, Hck, HGF receptor (Met), TEC, VEGFR-3, Fer, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, Ephrin-A receptor 4 | 262 | 2.063 × 10−79 |
| phosphate-containing compound metabolic process | PDGF-R-beta, PDGF receptor, ALS2CR7, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, BCKD, GCK(MAP4K2), Ephrin-B receptors, Ephrin-B receptor 2, p38gamma (MAPK12), p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, JNK(MAPK8-10), JNK1(MAPK8), MAPK8/9, PFTAIRE-1, DDR1, PDGF-R-alpha, p38beta (MAPK11), MYO3B, Lck, Ephrin-A receptor 6, FAK1, ENO3, ENO, ErbB2, LAT, **CDK3**, Insulin receptor, YES, PCTK2, p47-phox, NADPH oxidase, ZAP70, CaMK II, CaMK II beta, ROS1, PCTK1, **CDK2**, CaMK II gamma, JNK3(MAPK10), Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JNK2(MAPK9), JAK2, c-Src, STK36, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), FRK, ITK, MER, FGFR2, CaMK II alpha, **CDK1** (p34), BCKD-kinase, c-Fes, CALM3, CALM2, Calmodulin, ERK5 (MAPK7), ESR1 (nuclear), ESR1 (mitochondrial), ESR, ESR1 (membrane), STK4, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, c-Cbl, TrkC, ROR1, ULK3, unc-51-like kinase 3 (C. elegans), FGFR1, IRR, VEGFR-2, p38delta (MAPK13), Ephrin-A receptor 1, Ephrin-B receptor 1, MYO3A, Myosin IIIA, Myosin IIIA, GLK(MAP4K3), PP2A cat (alpha), PP2A catalytic, DCAMKL1, Ephrin-A receptor 2, PCTK3, LTK, Pyk2(FAK2), STK3, IGF-1 receptor, EGFR, ENO2, ErbB4, p120GAP, RET, MSP receptor (RON), **CDK5**, TrkA, FGFR3, Myelin basic protein, Hck, HGF receptor (Met), TEC, PLC-gamma, PLC-gamma 1, ENO1, VEGFR-3, Fer, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, PP2A cat (beta), c-Raf-1, Ephrin-A receptor 4, STAT4 | 2757 | 9.505 × 10−70 |
| phosphorus metabolic process | PDGF-R-beta, PDGF receptor, ALS2CR7, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, BCKD, GCK(MAP4K2), Ephrin-B receptors, Ephrin-B receptor 2, p38gamma (MAPK12), p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, JNK(MAPK8-10), JNK1(MAPK8), MAPK8/9, PFTAIRE-1, DDR1, PDGF-R-alpha, p38beta (MAPK11), MYO3B, Lck, Ephrin-A receptor 6, FAK1, ENO3, ENO, ErbB2, LAT, **CDK3**, Insulin receptor, YES, PCTK2, p47-phox, NADPH oxidase, ZAP70, CaMK II, CaMK II beta, ROS1, PCTK1, **CDK2**, CaMK II gamma, JNK3(MAPK10), Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JNK2(MAPK9), JAK2, c-Src, STK36, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), FRK, ITK, MER, FGFR2, CaMK II alpha, **CDK1** (p34), BCKD-kinase, c-Fes, CALM3, CALM2, Calmodulin, ERK5 (MAPK7), ESR1 (nuclear), ESR1 (mitochondrial), ESR, ESR1 (membrane), STK4, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, c-Cbl, TrkC, ROR1, ULK3, unc-51-like kinase 3 (C. elegans), FGFR1, IRR, VEGFR-2, p38delta (MAPK13), Ephrin-A receptor 1, Ephrin-B receptor 1, MYO3A, Myosin IIIA, Myosin IIIA, GLK(MAP4K3), PP2A cat (alpha), PP2A catalytic, DCAMKL1, Ephrin-A receptor 2, PCTK3, LTK, Pyk2(FAK2), STK3, IGF-1 receptor, EGFR, ENO2, ErbB4, p120GAP, RET, MSP receptor (RON), **CDK5**, TrkA, FGFR3, Myelin basic protein, Hck, HGF receptor (Met), TEC, PLC-gamma, PLC-gamma 1, ENO1, VEGFR-3, Fer, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, PP2A cat (beta), c-Raf-1, Ephrin-A receptor 4, STAT4 | 2884 | 2.410 × 10−67 |
| transmembrane receptor protein tyrosine kinase signaling pathway | PDGF-R-beta, PDGF receptor, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, Ephrin-B receptors, Ephrin-B receptor 2, p38gamma (MAPK12), p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, DDR1, PDGF-R-alpha, p38beta (MAPK11), Lck, Ephrin-A receptor 6, FAK1, ErbB2, LAT, Insulin receptor, YES, p47-phox, NADPH oxidase, ZAP70, ROS1, CD3, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JAK2, c-Src, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), FRK, ITK, FGFR2, c-Fes, Ephrin-A receptor 7, Ephrin-B receptor 3, c-Cbl, TrkC, ROR1, FGFR1, IRR, VEGFR-2, p38delta (MAPK13), Ephrin-A receptor 1, Ephrin-B receptor 1, Ephrin-A receptor 2, LTK, Pyk2(FAK2), IGF-1 receptor, EGFR, ErbB4, p120GAP, RET, MSP receptor (RON), TrkA, FGFR3, Hck, HGF receptor (Met), TEC, PLC-gamma, PLC-gamma 1, VEGFR-3, Fer, ALK, Ephrin-B receptor 4, TrkB, c-Raf-1, Ephrin-A receptor 4 | 695 | 1.263 × 10−65 |
| positive regulation of protein phosphorylation | PDGF-R-beta, PDGF receptor, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, GCK(MAP4K2), Ephrin-B receptors, Ephrin-B receptor 2, p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, JNK(MAPK8-10), MAPK8/9, DDR1, PDGF-R-alpha, p38beta (MAPK11), Lck, Ephrin-A receptor 6, FAK1, ErbB2, LAT, Insulin receptor, YES, p47-phox, NADPH oxidase, CaMK II, ROS1, JNK3(MAPK10), CD3, Ephrin-A receptor 5, Paxillin, DDR2, Syk, JNK2(MAPK9), JAK2, c-Src, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), Annexin II, MER, FGFR2, **CDK1** (p34), CALM3, CALM2, Calmodulin, ESR1 (nuclear), ESR1 (mitochondrial), ESR, ESR1 (membrane), STK4, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, TrkC, ROR1, FGFR1, IRR, VEGFR-2, Ephrin-A receptor 1, Ephrin-B receptor 1, GLK(MAP4K3), PP2A cat (alpha), PP2A catalytic, Ephrin-A receptor 2, LTK, Pyk2(FAK2), STK3, IGF-1 receptor, TCF7L2/ beta-catenin, Beta-catenin, PECAM1, EGFR, ErbB4, Epo receptor, p120GAP, RET, MSP receptor (RON), **CDK5**, TrkA, FGFR3, HGF receptor (Met), TEC, PLC-gamma, PLC-gamma 1, VEGFR-3, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, c-Raf-1, Ephrin-A receptor 4 | 1401 | 2.861 × 10−62 |
| cellular protein modification process | PDGF-R-beta, PDGF receptor, ALS2CR7, PDK (PDPK1), Ephrin-A receptor 3, Ephrin-A receptors, BCKD, GCK(MAP4K2), Ephrin-B receptors, Ephrin-B receptor 2, Annexin I, p38gamma (MAPK12), p38 MAPK, UFO, Lyn, SFK, Ephrin-A receptor 8, Fyn, VEGFR-1, JNK(MAPK8-10), JNK1(MAPK8), MAPK8/9, PFTAIRE-1, DDR1, PDGF-R-alpha, p38beta (MAPK11), MYO3B, Lck, HIST1H2BD, Histone H2B, HIST1H2BG, Histone H2, Ephrin-A receptor 6, FAK1, ENO, ErbB2, LAT, **CDK3**, Histone H2BO, Insulin receptor, YES, PCTK2, ZAP70, CaMK II, CaMK II beta, ROS1, HIST1H2BM, PCTK1, **CDK2**, H2BFQ, CaMK II gamma, JNK3(MAPK10), Wee1B, JAK1, Ephrin-A receptor 5, Paxillin, DDR2, Syk, HIST1H2BA, JNK2(MAPK9), HIST1H2BN, JAK2, c-Src, STK36, PI3K reg class IA, PI3K reg class IA (p85-alpha), PI3K reg class IA (p85), FRK, ITK, ZNF145, HIST1H2BL, MER, FGFR2, CaMK II alpha, **CDK1** (p34), BCKD-kinase, c-Fes, CALM3, CALM2, Calmodulin, ERK5 (MAPK7), ESR1 (nuclear), ESR1 (mitochondrial), ESR, ESR1 (membrane), STK4, Ephrin-A receptor 7, Tyro3, Ephrin-B receptor 3, c-Cbl, TrkC, ROR1, ULK3, unc-51-like kinase 3 (C. elegans), FGFR1, IRR, VEGFR-2, p38delta (MAPK13), Ephrin-A receptor 1, Ephrin-B receptor 1, MYO3A, Myosin IIIA, Myosin IIIA, GLK(MAP4K3), PP2A cat (alpha), PP2A catalytic, DCAMKL1, Ephrin-A receptor 2, PCTK3, LTK, Pyk2(FAK2), STK3, IGF-1 receptor, EGFR, ErbB4, p120GAP, RET, MSP receptor (RON), HIST1H2BK, Histone H2B type 1-K, Histone H2B type 1-K, **CDK**5, TrkA, FGFR3, Myelin basic protein, Hck, HGF receptor (Met), TEC, ENO1, VEGFR-3, Fer, HIST1H2BB, CaMK II delta, ALK, Ephrin-B receptor 4, TrkB, PP2A cat (beta), Desmoplakin, c-Raf-1, Ephrin-A receptor 4, STAT4, HIST1H2BJ | 4029 | 7.539 × 10−62 |

Link to the supplementary material **S3**= excel file

<https://1drv.ms/x/s!AuA2qju9wwwomVAXNqa51OxIj34U?e=vH03AE>

|  |  |  |
| --- | --- | --- |
|  |  | |
| control |
|  |  |  |
| HAA2020 500 nM | HAA2020 2500 nM | HAA2020 5000 nM |
|  |  |  |
| dina 5 nM | dina 25 nM | dina 50 nM |
|  |  |  |
| HAA2020 500 nM + dina 5 nM | HAA2020 2500 nM + dina 25 nM | HAA2020 5000 nM + dina 50 nM |

**Figure S4.** Histograms of cell cycle analysis in MCF7 cells. Cells were treated for 24 h with either HAA2020 (500, 2500, 5000 nM), dinaciclib (5, 25, 50 nM) or their combinations. Histograms of 20,000 events acquired on a BC-500 flow cytometer and analyzed by Expo 32 software, x-axis: DNA content, y-axis: % of cell number.

|  |  |  |
| --- | --- | --- |
|  |  | |
| control |  | |
|  |  |  |
| HAA2020 500 nM | HAA2020 2500 nM | HAA2020 5000 nM |
|  |  |  |
| dina 5 nM | dina 25 nM | dina 50 nM |
|  |  |  |
| HAA2020 500 nM + dina 5 nM | HAA2020 2500 nM + dina 25 nM | HAA2020 5000 nM + dina 50 nM |

**Figure S5.**  Histograms showing detection of apoptosis in MCF7 cells (24 h). Cells were treated with either HAA2020 (500, 2500, 5000 nM), dinaciclib (5, 25, 50 nM) or their combinations. Cells were stained with annexin V FITC/PI. A total of 20,000 single-cell events were acquired on a BC-500 flow cytometer and analyzed by Expo 32 software. Cell staining status: necrotic cells (C1: annexin V−/PI+), late apoptotic cells (C2: annexin V+/PI+), live cells (C3: annexin V−/PI−), early apoptotic cells (C4: annexin V+/PI−). Annexin V (x-axis), and PI staining (y-axis).