**New kinase and histone deacetylase hybrid inhibitors: recent advances and perspectives**

**Supplementary Material**

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**Table S1.** Hybrid RTK/HDAC inhibitors (**1-19**) developed in the last years.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **RTK**  **(IC50 or % inhibition)** | **HDAC**  **(IC50 or %)** | **Cells and *in vitro* assays**  **(IC50 or GI50)** | ***In vivo* assays** | **Ref** |
| **1** | VEGFR-2: 84 nM | HDACs: 2.8 nM  HDAC1: 3.5 nM HDAC8: 5.2 nM  HDAC2: 6.8 nM HDAC6: 25.5 nM | MCF-7: 1.2 µM  HCT-116: 1.8 µM  HepG2: 2.7 µM  A549: 5.4 µM | - | [1] |
| **2** | VEGFR-2: 74 nM | HDACs: 2.2 nM HDAC1: 1.8 nM HDAC2: 3.3 nM HDAC8: 4.6 nM  HDAC6: 16.4 nM | MCF-7: 0.85 µM | - | [2] |
| **3** | EGFR: 2.4 nM HER2: 15.7 nM | HDAC: 4.4 nM | Sk-Br-3: 0.04 μM  MDA-MB-231: 0.1 μM  HCC827: 0.6 μM H358: 0.6 μM H460: 0.7 μM  Capan1: 0.8 μM HepG2: 0.13 μM Sk-Hep-1: 0.22 μM  Hep3B2: 0.23 μM BxPc3: 0.27 μM MCF-7: 0.55 μM | Human Tumor Xenograft Models intravenous administration CAL-27 120 mg/kg: -36.5 regression  HepG2 120 mg/kg: -21.3 regression  MDA-MB468 120 mg/kg: -13,7 regression  Protein expression  ↑ acetylated H3 histone  ↓ phosphorylated EGFR  ↓ phosphorylated HER2 | [3] |
| **4** | EGFR: 1.2 μM HER2: 3.4 μM | HDAC: 34 nM HDAC3: 15 nM  HDAC8: 0.59 μM  HDAC1: 6.5 nM HDAC6: 7.3 nM | Cal27: 0.16 μM  SKBR3: 0.19 μM  A549: 0.24 μM  A431: 0.26 μM  HeLa: 0.5 μM  SKOV3: 0.56 μM | - | [4] |
| **5** | EGFR: 63.6%  at 10 μg/mL HER2: 74%  at 10 μg/mL | HDAC6: 1.66 μM  HDAC3: 2.38 μM HDAC1: 5.57 μM | - | - | [5] |
| **6** | EGFR: 0.69 nM HER-2: 176.7 nM | HDAC1: 0.65 nM HDAC6: 8.4 nM | A549: 0.51 µM  SK-BR-3: 1.27 µM  A431: 1.95 µM  BT-474: 3.63 µM  NCI-H1975: 8.76 µM | - | [6] |
| **7** | EGFR: 0.12 nM HER-2: 174.9 nM | HDAC1: 0.72 nM HDAC6: 3.2 nM | A431: 0.49 µM  A549: 0.63 µM  SK-BR-3: 0.69 µM BT-474: 3.88 µM NCI-H1975: 8.05 µM | - | [6] |

**(Table S1)** Contd…

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **RTK**  **(IC50 or % inhibition)** | **HDAC**  **(IC50 or %)** | **Cells and *in vitro* assays**  **(IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **8** | EGFR: 2.5 nM HER2: 4.1 nM  CDK2: 0.44 μM PDGF-Rβ: 3.3 μM InsR: 7.34 μM Abl1: 7.7 μM P1K1: 12.0 μM PKA: 120 μM | HDAC: 0.63 μM HDAC6: 0.23 μM  HDAC1: 0.61 μM HDAC3: 6.30 μM HDAC8: 11 μM | SKBR3: 0.51 μM Cal27: 0.82 μM  A431: 1.9 μM  SKOV3: 2.1 μM  HeLa: 3.2 μM  A549: 3.9 μM | - | [7] |
| **9** | EGFR: 0.018 μM HER2: 0.011 μM PDGF-Rβ: 2.5 μM InsR: 3.6 μM Abl1: 5.3 μM CDK2: 0.92 μM PKA: > 100 μM P1K1: 6.8 μM | HDAC: 47 nM HDAC1: 35 nM HDAC3: 66 nM HDAC6: 86 nM HDAC8: 0.63 μM | A549: 1.2 μM HeLa: 0.97 μM A431: 0.72 μM Cal27: 0.59 μM SKOV3: 1.0 μM SKBR3: 0.35 μM | - | [7] |
| **10** | EGFR: 0.90 μM | HDAC: 1.21 μM | A431: 1.88 μM A549: 15.5 μM HL-60: 30.9 μM | - | [8] |
| **11** | EGFR: 1.56 μM | HDAC: 1.09 μM | A431: 6.46 μM HL-60: 9.83 μM  A549: 24.1 μM | - | [8] |
| **12** | EGFR (T790M):  5.0 µM  EGFR (WT):  5.7 µM | HDACs: 0.085 µM | MDA-MB-468: 0.23 µM  KG-1: 0.24 µM  MDA-MB-231: 0.60 µM  HT-29: 0.79 µM  HeLa: 1.85 µM  A549: 2.19 µM PC-3: 3.39 µM | - | [9] |
| **13** | VEGFR-1: 35 nM  VEGFR-2: 46 nM PDGFRβ: 0.111 µM VEGFR-3: 0.113 µM C-kit: 0.163 µM FGFR1: 0.409 µM C-Fms: 0.581 µM | HDACs: 3.3 nM HDAC6: 72 nM  HDAC2: 0.38 µM HDAC8: 1.66 µM | MOLT-4: 0.31 µM  K562: 0.99 µM  KG1: 1.60 µM  PC-3: 1.69 µM  HT-1080: 1.97 µM  HT-29: 2.51 µM HEL: 2.80 µM MDA-MB-231: 2.96 µM  AGS: 4.44 µM HeLa: 4.36 µM ACHN: >5 µM |  | [10] |
| **14** | VEGFR-1: 22 nM  VEGFR-2: 37 nM  VEGFR-3: 46 nM PDGFRβ: 88 nM FGFR1: 0.192 µM C-Fms: 0.351 µM C-kit: 0.125 µM | HDACs: 4.6 µM HDAC1: 0.59 µM HDAC2: 0.91 µM HDAC3: 0.43 µM | KG1: 0.67 µM  MOLT-4: 0.94 µM  HT-29: 1.07 µM  HEL: 1.52 µM HeLa: 1.71 µM  K562: 1.82 µM PC-3: 2.38 µM MDA-MB-231: 3.74 µM ACHN: >5 µM AGS: >5 µM  HT-1080: >5 µM | oral administration t1/2: 2.10 h Cmax: 3252 ng/mL Tmax: 0.5 h F: 72% 13 hydrochlorate, 50 mg/kg/day, 25 days, HT-29 xenograft model in mice  TGI: 40% | [10] |
| **15** | c-Met: 0.71 nM | HDAC1: 38 nM | EBC-1: 58 nM HCT-116: 1.3 µM | - | [11] |
| **16** | c-Met: 12.5 nM | HDAC1: 26.97 nM | MCF-7: 0.28 µM  HCT-116: 0.54 µM A549: 1.08 µM | - | [12] |
| **17** | c-Met: 21.44 μM | HDAC: 45.22 μM | MCF-7: 0.60 μM A549: 0.85 μM | - | [13] |
| **18** | FGFR1: 64%  at 1 µM | HDAC6: 34 nM HDAC8: 88% at 1µM  HDAC1: 59% at 1µM | MCF-7: 9.0 µM | - | [14] |
| **19** | EphA2: 0.57 µM | HDACs: 1.52 µM | HCT116: 5.29 µM MCF-7: 7.42 µM  K562: 9.17 µM | - | [15] |

**Table S2.** Hybrid non-receptor TK/HDAC inhibitors **20 28**) developed in the last years.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **TK**  **(IC50 or %)** | **HDAC**  **(IC50 or %)** | **Cells**  **(IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **20** | Bcr-Abl: 21.2 nM | HDAC1: 0.126 µM  HDAC6: 28.27 µM  HDAC3: no activity  HDAC8: no activity | K562: 2.56 µM DU145: 5.9 µM  Hepg2: 16.53 µM | - | [16] |
| **21** | Bcr-Abl: 17.8 nM | HDAC1: 0.810 µM HDAC3: 40.48 µM HDAC6: no activity HDAC8: no activity | DU145: 0.60 µM  K562: 2.62 µM Hepg2: 10.44 µM | - | [16] |
| **22** | JAK2: 33 nM | HDAC6: 1.3 nM  HDAC1: 89 nM | KMS-12-BM: 70 nM  MDA-MB-231: 1.02 µM  Jukat: 1.03 µM  HCT-116: 1.15 µM XG-6: 1.07 µM  HEL92.1.7: 1.36 µM PC-3: 1.51 µM MCF7: 2.01 µM | - | [17] |
| **23** | JAK2: 3.1 nM TYK2: 9.4 nM  JAK1: 52.1 nM JAK3: 80.1 nM | HDAC6: 1.2 nM  HDAC1: 56 nM | PC-3: 0.64 µM  MCF7: 0.70 µM MDA-MB-231: 0.99 µM  HCT-116: 1.05 µM | - | [17] |
| **24** | JAK2: 1.4 nM JAK1: 8.7% at 0.1 μM JAK3: 55% at 0.1 μM TYK2: 56% at 0.1 μM FLT3: 67% at 0.1 μM | HDAC6: 2.1 nM  HDAC2: 46 nM HDAC10: 80 nMHDAC1: 0.222 μM HDAC8: 0.7 μM HDAC11: 0.93 μM HDAC3: 2.17 μM | HEL92.1.7: 0.94 μM  NKYS: 1.08 μM KHYG: 1.09 μM  MOLM-14: 1.14 μM Jukat: 1.19 μM  MDA-MB-231: 1.43 μM MCF-7: 1.47 μM  KG-1: 1.63 μM  PC-3: 1.7 μM  OPM-2: 2.05 μM  KMS-12-BM: 2.11 μM HCT-116: 2.23 μM Toxicity TAMH: 9.57 μM  Therapeutic window: 8.7 Microssomal stability t1/2: 17.3 min  (male rat) t1/2: 26.3 min  (female rat) Clint,app: 16.3 L/h/kg (male rat) Clint,app: 10.7 L/h/kg (female rat) | - | [18] |
| **25** | JAK2: 4 nM JAK1: 4.8 nM JAK3: 7.4 nM TYK2: 49 nM | HDAC6: 14 nM HDAC2: 0.12 µM HDAC8: 2.47 µM | MOLT4: 80 nM  Jukat: 60 nM  HEL: 90 µM K562: 0.49 µM Microsomal stability phase I t1/2: 25.8 min (human) phase II t1/2: 361.1 (human) | oral administration (10 mg/kg) t1/2: - h Tmax: 0.30 h Cmax: 6.8 ng/mL F: < 1 % HEL xenograft model, 100 mg/kg/day intraperitoneal, 16 days TGI: 36% | [19] |

**(Table S2)** Contd…

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **TK**  **(IC50 or %)** | **HDAC**  **(IC50 or %)** | **Cells**  **(IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **26** | JAK2: 8 nM  JAK2: 8.4 nM  TYK2: 46 nM JAK1: 359 nM JAK3: 121 nM | HDAC6: 46 nM  HDAC3: 234 nM HDAC1: 1.1 µM  HDAC8: 6.06 µM  HDAC2: 7.5 µM | HEL: 0.34 µM  HL-60: 1.5 µM K562: 8.7 µM Microsomal stability t1/2: 19.4 min CL: 0.0716 mL/min/mg | Intraperitoneal administration (10 mg/kg), SD rats  t1/2: 5.14 h Cmax: 2603.41 ng/mL   HEL AML xenograft model in mice Intraperitoneal administration (10 mg/kg), once a day extended lifetime and survival. After 32 days 20a treated mice presented 37.5% survival | [20] |
| **27** | JAK1: 14 nM  JAK2: 75 nM TYK2: 0.188 µM  JAK3: 0.569 µM | HDAC6: 1.4 nM HDAC3: 3.9 nM  HDAC2: 5.8 nM  HDAC1: 6.9 nM HDAC10: 19 nM HDAC11: 31 nM HDAC8: 0.469 µM HDAC5: 10.5 µM HDAC7: 17.2µM | KG-1: 0.15 µM  NKYS: 0.45 µM  MV4-11: 0.46 µM Jukart: 0.47 µM  KHYG: 0.57 µM  MOLM-14: 0.74 µM MDA-MB-231: 0.79 µM MCF7: 0.84 µM HEL92.1.7: 1.33 µM XG-6: 2.01 µM  KMS-12-BM: 2.02 µM OPM-2: 2.16 µM  HCT-116: 2.32 µM PC3: 2.41 µM Hl-60: 7.36 µM | oral administration (5 mg/kg) t1/2:0.58 h Tmax: 0.0083 h Cmax: 15.9 ng/mL F: 1.4 % | [21] |
| **28** | **Ki values** c-Src: 138 nM Hck: 504 nM  c-Abl: 2350 nM | HDAC6: 2.7 nM  HDAC3: 19 nM  HDAC10: 51 nM  HDAC1: 86 nM HDAC11:224 nM  HDAC2: 231 nM  HDAC8: 2.311 μM HDAC4: 3.982 μM HDAC5: 3.891 μM HDAC7: 13.22 μM HDAC9: 28.02 μM | MALME-3M: 0.07 μM  HS 578T: 0.17 μM HCT-116: 0.22 μM SW-620: 0.25 μM U251: 0.28 μM  MCF7: 0.35 μM DU-145: 0.39 μM  MDA-MB-231: 0.39 μM KM12: 0.47 μM | - | [22] |

**Table S3.** Hybrid SK/HDAC inhibitors (**29-39**) developed in the last years.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cpd.** | **SK**  **(IC50 or %)** | **HDAC**  **(IC50 or %)** | **Cells and *in vitro* assays (IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **29** | BRafV500E: 73 nM CRaf: 92 nM  ARaf: 0.183 μM | HDAC1: 1.17 μM HDAC6: no activity  HDAC8: no activity | MDA-MB-468: 0.57 μM  MV4-11: 1.12 μM Hepg2: 1.33 μM  K562: 2.73 μM | - | [23] |
| **30** | BRafV500E: 86 nM ARaf: 45 nM CRaf: 0.102 μM  Braf WT: 0.134 μM | HDAC1: 1.71 μM HDAC6: N. A. HDAC8: N.A. | MV4-11: 0.38 μM  SK-Mel-2: 5.4 μM A549: 9.11 μM  K562: 9.13 μM HCT116: 10.87 μM | - | [24] |
| **31** | CDK2: 0.56 μM  CDK1: 12.58 μM CDK4: >1000 μM CDK6: >1000 μM CDK7: >1000 μM | HDAC2: 0.24 μM HDAC1: 240 μM HDAC3: >1000 μM HDAC6: >1000 μM HDAC8: >1000 μM | HCT116: 1.45 μM A375: 1.60 μM H460: 2.63 μM Hela: 3.15 μM  NIH 3T3: 4.64 μM SMMC7721: 5.22 μM | intraperitoneal administration (20 mg/kg) mice t1/2: 1.63 hF: 27.8 % | [25] |

**(Table S3)** Contd…

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cpd.** | **SK**  **(IC50 or %)** | **HDAC**  **(IC50 or %)** | **Cells and *in vitro* assays (IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **32** | CDK2: 0.30 μM  CDK1: 8.43 μM CDK4: >1000 μM CDK6: >1000 μM CDK7: >1000 μM | HDAC2: 0.25 μM HDAC1: 6.4 μM HDAC3: 45 μM HDAC6: >1000 μM HDAC8: >1000 μM | HCT116: 0.71 μM A375: 1.20 μM Hela: 1.83 μM H460: 4.19 μM NIH 3T3: 4.47 μM | intraperitoneal administration (20 mg/kg) mice t1/2: 2.61 h F: 63.6 % HCT116 xenograft model in mice, intraperitoneal administration (25 mg/kg dose), 21 days TGI: 51.0 % | [25] |
| **33** | CDK2: 56 nM | HDAC1: 5.8 nM | HepG2: 0.77 μM CAL-148 1.14 μM  A549: 1.49 μM | - | [26] |
| **34** | CDK2: 127 nM | HDAC1: 7.0 nM | HepG2: 0.22 μM CAL-148 0.39 μM  A549: 1.26 μM | - | [26] |
| **35** | CDK4: 8.8 nM CDK9: 9 nM | HDAC1: 2.2 nM | 4T1: 1.11 μM  Hep3B: 1.24 μM  A549: 1.33 μM  MDA-MB-468: 1.82 μM MDA-MB-231: 1.86 μM H1299: 1.87 μM T47D: 2.59 μM HepG2: 3.37 μM H460: 3.78 μM | oral administration (20 mg/kg) Cmax: 136.8 μg/L Tmax: 1.8 F: 18.4 % t1/2: 14.91 h 4T1 murine breast cancer in BALB/c mice, daily treatment, oral administration, 24 days 90 mg/kg: 70.3% TGI 130 mg/kg: 79.3% TGI | [27] |
| **36** | CK2α: 61.6 % at 50 μM | HDAC1: 2.2 μM | Jurkat: 2.87 μM MCF-7: 4.26 μM HaCat: 13.66 μM 293T: 14.55 μM | - | [28] |
| **37** | CK2: 5.89 μM | HDAC6: 8.98 μM HDAC1: 13.7 μM | HL-60/vinc: 2.32 μM HCT-116: 3.10 μM  Jurkat: 5.30 μM HL-60/adr: 8.4 μM HEK293: 8.41 μM  HL-60: 4.69 μM  MCF-7: 9.02 μM | - | [29] |
| **38** | CDK4: 1.2 nM CDK6/cyclinD3: 97 % at 1 μM JAK1: 22 nM | HDAC6: 5.9 nM  HDAC1: 26 nM  HDAC3: 56 nM  HDAC10: 73 nM HDAC2: 0.52 μM HDAC11: 6.8 μM HDAC4: >10 μM HDAC5: >10 μM HDAC7: >10 μM HDAC8: >10 μM HDAC9: >10 μM | OVCAR-5 15.8 nM 4T1: 18.3 nM MDA-MB-231: 23.9 nM  MDA-MB-468: 32.3 nM  SK-OV-3: 44 nM H460: 32.77 nM | oral administration (10 mg/kg) rat model t1/2: 8.361 h Tmax: 4 h Cmax: 0.803 mg/L F: 77.39% | [30] |
| **39** | mTOR: 1.2 nM | HDAC1: 0.19 nM HDAC10: 0.58 nM HDAC2: 0.61 nM  HDAC8: 1.28 nM HDAC3: 1.47 nM HDAC6: 1.8 nM HDAC4: >1000 nM HDAC5: >1000 nM  HDAC7: > 1000 nM  HDAC9: >1000 nM HDAC11: >1000 nM | leukemia MV4-11: 4.05 nM OCI-AML2: 9.01 nM OCI-AML3: 9.98 nM | intravenous administration (20 mg/kg, Q2D x 5) MM1S xenograft NOD/SCID mice model survivors: 6/6 TGI: 72.5% | [31] |

**Table S4:** Hybrid LK/HDAC inhibitors (**40-46**) developed in the last years.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **LK  (IC50 or %)** | **HDAC  (IC50 or %)** | **Cells and *in vitro* assays (IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **40** | PI3Kα: 19 nM PI3Kδ: 39 nM PI3Kβ: 54 nM  PI3Kγ: 311 nM | HDAC1: 1.7 nM HDAC3: 1.8 nM  HDAC10: 2.8 nM  HDAC2: 5.0 nM HDAC11: 5.4 nM HDAC6: 27 nM HDAC8: 191 nM HDAC4: 409 nM  HDAC7: 426 nM  HDAC9: 554 nM HDAC5: 674 nM | MV-4-11: 0.4 nM  SUP-B15: 0.7 nM  DOHH2: 1 nM  HH: 1 nM HuT78: 1 nM  MDA-MB-361: 1 nM  MOLT4: 1 nM  OPM-2: 1 nM  HL60: 2 nM RL: 2 nM  RPMI-8226: 2 nM U937: 2 nM  SU-DHL4: 3 nM  Pfeiffer: 4 nM ARH77: 5 nM  MJ: 5 nM  SW620: 5 nM  BT474: 6 nM  HCC1500: 6 nM  MEG-01: 6 nM  SW116: 6 nM  Granta 519: 7 nM  HCC1806: 7 nM  HCT-116: 7 nM  MDA-MB-453: 7 nM  SW403: 7 nM  H292: 8 nM H2122: 8 nM  MCF-7: 8 nM  SW1990: 8 nM  H358: 9 nM  Raji: 9 nM  A549: 10 nM  UACC-893: 10 nM Daudi: 15 nM THP-1: 16 nM  Calu6: 20 nM  CaPan2: 20 nM  MiaPaca2: 20 nM T47D: 20 nM  T-84: 30 nM K562: 31 nM WiDr: 40 nM  CFPAC-1: 50 nM  H460: 50 nM  PANC-1: 50 nM  SKBr3: 50 nM  ZR-75-1: 80 nM MDA-MB-468: 90 nM MDA-MB-231: 0.12 µM | Daudi NHL xenograft mouse model (100 mg/kg), oral and intravenous administration plasma t1/2: 7.7 h  tumor t1/2: 12.6 h  tumor stasis was observed   SU-DHL4 diffuse large B-cell lymphoma xenograft mouse model, oral administration (100 mg/kg) or intravenous administration (50 mg/kg) tumor stasis or tumor regression observed  A549 bearing mutant KRAS xenograft mouse model, oral administration (100 mg/kg) or intravenous administration (50 mg/kg) tumor stasis observed  Protein expression  ↑ acetylated H3 histone  ↓ phosphorylated Akt  ↓ phosphorylated MAPK  ↓ phosphorylated ERK | [32] |
| **41** | PI3Kα: 1.33 nM PI3Kδ: 8.10 nM PI3Kγ: 15 nM  PI3Kβ: 34 nM | HDAC1: 1.04 nM HDAC2: 2.62 nM  HDAC10: 2.83 nM HDAC3: 3.29 nM HDAC6: 22 nM HDAC8: 22 nM HDAC5: 484 nM HDAC7: 650 nM  HDAC4: 653 nM  HDAC9: >1 µM HDAC11: >1 µM | HeLa: 3.30 nM MV4-11: 7.65 nM A2780: 117.6 nM HCT116: 214.2 nM | intravenous administration (10 mg/kg, Q2D x 11) MV4-11 xenograft NOD/SCID mice model Tumor mass change: 45.1 % Weight loss: 6.4 % at day 13 Survivors: 4/6 | [33] |

**(Table S4)** Contd…

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **LK  (IC50 or %)** | **HDAC  (IC50 or %)** | **Cells and *in vitro* assays (IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **42** | PI3Kα: 3.5 nM  PI3Kδ: 37 nM  PI3K2β: 103 nM PI3Kγ: 177 nM  PI3Kβ: 212 nM PI3K2α: >1 µM mTOR: 1.946 µM DNA-PK: 10 µM PIK3C3: 10 µM PI4Kβ: > 10 µM | HDAC1: 1.1 nM  HDAC3: 1.1 nM  HDAC10: 2.5 nM  HDAC6: 4.2 nM  HDAC2: 6.0 nM HDAC8: 320 nM HDAC9: 1.282 µM HDAC7: 2.305 µM  HDAC4: 4.591 µM HDAC5: 4.8 µM HDAC11: 9.7 µM | MV4-11: 47 nM MOLT4: 0.14 μM  SU-DHL-6: 0.19 μM  Raji: 0.24 μM  K562: 0.35 μM Ramos: 0.40 μM  HuH-7: 0.48 μM HepG2: 0.59 μM SK-HEP1: 0.79 μM PC-3: 1.08 μM PLC/PRF/5: 1.24 μM Hep3B:1.25 μM SNU-398: 1.38 μM  SNU-387: 2.64 μM | oral administration (150 mg/kg), BALB/c mice model Tmax: 0.5 h t1/2: 4.41 h Cmax: 10.1 μM F: 18.1 %  Maximum tolerable dose MTD: 200 mg/kg QD x 5  oral administration (150 mg/kg QD x 5/wk x 4), HepG2 CB17 Sid Mice Xenograft Model TGI: 110% at day 26  Protein expression  ↑ acetylated H3 histone  ↓ phosphorylated Akt/mTOR | [34] |
| **43** | PI3Kα: 46.3 nM PI3Kβ: 72.8 nM PI3Kδ: 72.4 nM  mTOR: 464 nM PI3Kγ: 1300 nM | HDAC6: 15.3 nM HDAC8: 67.6 nM  HDAC1: >3 µM HDAC4: >3 µM HDAC11: >3 µM | - | - | [35] |
| **44** | PI3Kδ: 8.1 nM  PI3Kγ: 67 nM  PI3Kα: 68 nM PI3Kβ: 101 nM mTOR 2.861 µM | HDAC1: 1.4 nM HDAC2: 3.0 nM  HDAC6: 6.6 nM HDAC8 18 nM  HDAC4: >1 µM HDAC11: >1 µM | HGC-27: 0.11 μM  HCT116: 0.15 μM  MDA-MB-453: 0.30 μM HCT-8: 0.32 μM  Capan2: 0.43 μM  DU145: 0.54 μM SW1990: 0.90 μM  NCI-H1299: 1.0 μM  HepG2: 1.1 μM  MCF-7: 2.0 μM  Huh7: 2.5 μM  NCI-H460: 3.0 μM  U87: 3.2 μM  BEL-7402: 5.2 μM  THP-1: 5.4 μM K562: 6.8 μM hERG: > 30 μM | oral administration (30 mg/kg), ICR mice model t1/2β: 2.07 h Tmax: 0.30 h Cmax: 143 ng/mL F: 4.2 % Maximum tolerable dose in mice model (oral administration) MTD > 2000 mg/kg  oral administration (200 mg/kg), HGC-27 BALB/c Mice Xenograft Model TGI: 45.9%  Protein expression  ↑ acetylated H3 histone  ↓ phosphorylated Akt | [36] |
| **45** | PI3Kδ: 29 nM  PI3Kα: 226 nM PI3Kβ: 279 nM PI3Kγ: 467 nM mTOR 6.262 µM | HDAC1: 1.3 nM HDAC2: 3.4 nM HDAC8 12 nM HDAC6: 17 nM HDAC4: 972 nM HDAC11: > 1 µM | MDA-MB-453: 4 nM  HCT116: 7 nM  HGC-27: 14 nM  HCT-8: 59 nM  DU145: 66 nM HepG2: 76 nM NCI-H1299: 0.18 μM SW1990: 0.23 μM Huh7: 0.24 μM  Capan2: 0.27 μM  U87: 0.34 μM  THP-1: 0.91 μM MCF-7: 1.1 μM K562: 1.2 μM  BEL-7402: 1.6 μM NCI-H460: 2.7 μM hERG: > 30 μM | oral administration (30 mg/kg), ICR mice model t1/2β: n/d Tmax: 1.80 h Cmax: 9.39 ng/mL F: 1.7 %  Maximum tolerable dose in mice model MTD > 2000 mg/kg oral administration | [36] |

**(Table S4)** Contd…

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **LK  (IC50 or %)** | **HDAC  (IC50 or %)** | **Cells and *in vitro* assays (IC50, GL50 or LD50)** | ***In vivo* assays** | **Ref** |
| **46** | PI3Kγ: 7.0 nM  PI3Kδ: 9.0 nM  PI3Kα: 47 nM PI3Kβ: no activity | HDAC6: 12 nM  HDAC11: 463 nM  HDAC8: 611 nM HDAC7: 830 nM  HDAC4: 3.849 µM HDAC5: 5.239 µM  HDAC9: 7.246 µM  HDAC1: 11.11 µM HDAC3: 12.21 µM HDAC2: no activity  HDAC10: no activity | CCRM-CEM: 0.7 μM  SNB-75: 0.7 μM SR: 0.7 μM  HOP-92: 0.9 μM  A498: 1.0 μM  OVCAR3: 1.2 μM  RXF 393: 1.2 μM  T-47D: 1.2 μM  CAKI-1: 1.3 μM IGROV1: 1.5 μM LOX IMVI: 1.6 μM KM-12: 1.7 μM U251: 1.7 μM  M14: 1.8 μM  MDA-MB-231/ATCC: 1.8 μM U266: 1.9 μM  HS 578T: 2.0 μM HCT-2998: 2.1 μM  RPMI 8226: 2.1 μM HL-60: 2.4 μM  HOP-62: 2.4 μM  MOLM-14: 2.4 μM  MV4-11: 2.5 μM U937: 2.6 μM K562: 4.6 μM Microssomal stability HLM: 22.4 min MLM: 51.7 min RLM: 100.6 min | oral administration (10 mg/kg), BALC/c mice t1/2: 1.4 h Tmax: 0.167 h Cmax: 18.4 ng/mL F: 0.7 % intraperitoneal administration (150 mg/kg), BALC/c mice t1/2: 1.7 h Tmax: 2 h Cmax: 7783 ng/mL | [37] |

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