Description: A-674563 is an orally available, ATP-competitive, and reversible inhibitor of Akt (Ki: 11 nM for Akt1) [1]. It exhibits inhibitory activity against PKA and Cdk2 (IC50: 16/46 nM) but is 10- to >1,800-fold selective for Akt1 versus additional kinases in the CMGC, CAMK, and TK families [1].

Storage: 2 years -80°C in solvent; 3 years -20°C powder;

**Receptor (IC50)**

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<th>Akt1</th>
<th>CDK2</th>
<th>PKA</th>
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**In vitro Activity**

A-674563 reduces phosphorylation of Akt downstream targets in cells and slows proliferation of tumor cells in vitro (EC50: 0.4 μM) [1]. A563 (0-10 μM) markedly decreases GSK3 and MDM2 phosphorylation in STS cells. A563 shows inhibitory effect on all STS cell lines, with IC50 values at 48 hours ranging from 0.22 μM to 0.35 μM. A563 induces G2 cell cycle arrest and apoptosis in STS cells. A563 (1 μM/12 hr) upregulates the expression of GADD45A independent of p53[2]. A-674563 (10-1000 nM) is anti-proliferative and cytotoxic in cultured human melanoma cells, induces melanoma cell apoptotic death, inhibited by caspase inhibitors, and inhibits melanoma cells via Akt-dependent and -independent mechanisms[3]. A-674563 is cytotoxic and anti-proliferative when added to U937 and AML progenitor cells activate caspase-3/9 and apoptosis in U937 and AML progenitor cells and manipulate other signalings in AML cells while blocking Akt[4].

**In vivo Activity**

In the PC-3 prostate cancer xenograft model, A-674563 (40 mg/kg/d, p.o.) has no marked monotherapy activity, but the efficacy of the combination therapy (A-674563+paclitaxel) is significantly improved. In an oral glucose tolerance test, A-674563 (20, 100 mg/kg) can increase plasma insulin[1]. A563 (20 mg/kg/bid; p.o.) exhibits slow tumor growth and a significant difference in tumor volume without significant weight loss of mice. A563-treated tumors express increased levels of GADD45α and decreased levels of PCNA (a nuclear marker for proliferation). Additionally, TUNEL assay staining levels (marker for apoptosis) increase in the A563-treated specimens[2]. A-674563 (25, 100 mg/kg, lavage daily) effectively inhibits A375 xenograft growth in mice[3]. A-674563 (15, 40 mg/kg) injection inhibits U937 xenograft in vivo growth and improves mice survival[4].

Reference


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