# Data Sheet

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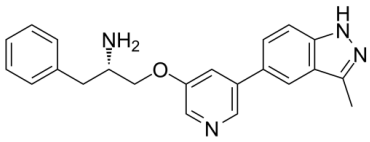
| **Product Name:** | A-674563 |
| **Cat. No.:** | CS-0486 |
| **CAS No.:** | 552325-73-2 |
| **Molecular Formula:** | $C_{22}H_{22}N_4O$ |
| **Molecular Weight:** | 358.44 |
| **Target:** | Akt |
| **Pathway:** | PI3K/Akt/mTOR |
| **Solubility:** | DMSO : 83.33 mg/mL (232.48 mM; Need ultrasonic) |




## BIOLOGICAL ACTIVITY:

A-674563 is an orally active and selective **Akt1** inhibitor with a $K_i$ of 11 nM. IC50 & Target: Ki: 11 nM (Akt1)[1] **In Vitro:** A-674563 slows proliferation of tumor cells with an $EC_{50}$ of 0.4 μM[1].

A563 (0-10 μM) significantly decreases GSK3 and MDM2 phosphorylation in STS cells. A563 shows inhibitory effect on all STS cell lines, with $IC_{50}$ values at 48 hours ranging from 0.22 μM (SW684) to 0.35 μM (SKLMS1). 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, activates caspase-3/9 and apoptosis in U937 and AmL progenitor cells, and manipulates other signalings in AmL cells whiling blocking Akt[4]. **In Vivo:** A-674563 (40 mg/kg/d, p.o.) shows no significant monotherapy activity, but the efficacy of the combination therapy (A-674563+paclitaxel) is significantly improved in the PC-3 prostate cancer xenograft model. A-674563 (20, 100 mg/kg) increases plasma insulin in an oral glucose tolerance test[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) potently 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].

## PROTOCOL (Extracted from published papers and Only for reference)

**Cell Assay:** [1]The cells on 96-well plates are gently washed with 200 μL of PBS. Alamar Blue reagent is diluted 1:10 in normal growth media. The diluted Alamar Blue reagent (100 μL) is added to each well on the 96-well plates and incubated until the reaction is complete. Analysis is done using an fmax Fluorescence Microplate Reader, set at the excitation wavelength of 544 nm and emission wavelength of 595 nm. Data are analyzed using SOFTmax PRO software. **Animal Administration:** A-674563 is formulated in 5% dextrose.[1]Immunocompromised male scid mice are at 6 to 8 weeks of age. The $1\times10^6$ 3T3-Akt1 or $2\times10^6$ MiaPaCa-2 and PC-3 cells in 50% Matrigel are inoculated s.c. into the flank. For early treatment studies, mice are randomLy assigned to treatment groups and therapy is initiated the day after inoculation. Ten animals are assigned to each group, including controls. For established tumor studies, tumors are allowed to reach a designated size and mice are assigned to treatment groups of equal tumor size (n=10 mice per group). Tumor size is evaluated by twice weekly measurements with digital calipers. Tumor volume is estimated using the formula: $V=L\times W^2/2$. A-443654 is given s.c. in a vehicle of 0.2% HPMC. A-674563 is given orally in a vehicle of 5% dextrose.

Gemcitabine and paclitaxel are added to the assay.

## References:


[1]. Luo Y, et al. Potent and selective inhibitors of Akt kinases slow the progress of tumors in vivo. Mol Cancer Ther, 2005, 4(6), 977-986.

[2]. Zhu QS, et al. Soft tissue sarcoma cells are highly sensitive to AKT blockade: a role for p53-independent up-regulation of GADD45 alpha. Cancer Res, 2008, 68(8), 2895-2903.

[3]. Zou Y, et al. Pre-clinical assessment of A-674563 as an anti-melanoma agent. Biochem Biophys Res Commun. 2016 Aug 12;477(1):1-8.

[4]. Xu L, et al. Concurrent targeting Akt and sphingosine kinase 1 by A-674563 in acute myeloid leukemia cells. Biochem Biophys Res Commun. 2016 Apr 15;472(4):662-8.

[5]. Wang A, et al. Dual inhibition of AKT/FLT3-ITD by A674563 overcomes FLT3 ligand-induced drug resistance in FLT3-ITD positive AML. Oncotarget. 2016 May 17;7(20):29131-42.


## CAIndexNames:

Benzeneethanamine, a-[[[5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]methyl]-, (aS)-

## SMILES:

N[C@@H](CC1=CC=CC=C1)COC2=CC(C3=CC4=C(C=C3)NN=C4C)=CN=C2

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