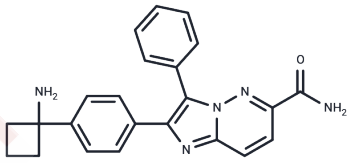
Data Sheet (Cat.No.T7315)

TargetMol

BAY1125976

Chemical Properties



CAS No. : 1402608-02-9

Formula: C23H21N5O

Molecular Weight: 383.45

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	BAY1125976 is an allosteric inhibitor of Akt1 and Akt2 (IC50s of 5.2 and 18 nM, respectively, in a time-resolved FRET assay)
Targets(IC50)	Akt
In vitro	In vitro, BAY1125976 inhibited cell proliferation in a broad panel of human cancer cell lines. Particularly high activity was observed in breast and prostate cancer cell lines expressing estrogen or androgen receptors.
In vivo	BAY1125976 exhibited strong in vivo efficacy in both cell line and patient-derived xenograft models such as the KPL4 breast cancer model (PIK3CAH1074R mutant), the MCF7 and HBCx-2 breast cancer models and the AKTE17K mutant driven prostate cancer (LAPC-4) and anal cancer (AXF 984) models. Indicate that BAY 1125976 is a potent and highly selective allosteric AKT1/2 inhibitor that targets tumors displaying PI3K/AKT/mTOR pathway activation, providing opportunities for the clinical development of new, effective treatments.
Kinase Assay	The inhibition of five different recombinant AKT proteins (AKT1, ΔPH-AKT1, AKT2, ΔPH-AKT2 and AKT3) by BAY 1125976 was assessed by TR-FRET-based in vitro kinase assays, which quantify the phosphorylation of the biotinylated peptide biotin-Ahx-KKLNRTLSFAEPG (C-terminus in amide form) by a recombinant kinase enzyme. The ability of BAY 1125976 to inhibit T308 phosphorylation in inactive AKT1 by the upstream kinase PDK1 was measured by a TR-FRET-based in vitro kinase assay. To further characterize the interaction of BAY 1125976 with human full-length active AKT1 and inactive AKT1, as well as a variant lacking the PH domain, surface plasmon resonance spectroscopy (SPR) was performed by a Biacore T100 instrument.
Animal Research	Female NMRI (nu/nu) mice s.c. injected with 3 × 10^6/100 µl KPL-4 breast cancer cells were used to study the mode-of-action of BAY 1125976. The treatment was started when tumors reached 232–358 mm^3 in size and the mice received a single oral dose of 25 or 50 mg/kg BAY 1125976. For determination of plasma concentration-time profiles, blood was drawn from the animals at different time points after compound administration. Analysis of the samples was performed on heparinized plasma after precipitation with acetonitrile by LC/MS/MS. Unbound drug concentrations were calculated from total concentrations and the unbound in vitro fraction in plasma was determined by equilibrium analysis. P-AKT-S473 levels in tumor tissue extracts were analyzed with a MULTI-SPOT Assay System/Phospho (Ser473)/Total Akt Whole Cell

Animal Research	Lysate Kit from samples taken 2, 5 and 24 hr after compound administration. These lysates were used in addition for analysis of p-PRAS40-T246/total-PRAS40 and AKT signaling (p-AKT-S473, p-GSK3?-S9, p-S6RP-S240/244 and p-70S6K-T389) using respective MULTI-SPOT Assay Systems. Vehicle-treated tumors were analyzed to determine the basal level of p-AKT and used to normalize the amount of p-AKT relative to vehicle levels.

Solubility Information

Solubility	DMSO: 25 mg/mL (65.2 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+90% Saline: < 2.5 mg/mL (6.52 mM),Lower concentrations may be soluble, but exact solubility limit is unknown. 10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2.5 mg/mL (6.52 mM),Solution. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.6079 mL	13.0395 mL	26.079 mL
5 mM	0.5216 mL	2.6079 mL	5.2158 mL
10 mM	0.2608 mL	1.304 mL	2.6079 mL
50 mM	0.0522 mL	0.2608 mL	0.5216 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Politz O , Siegel F , Bärfacker L, et al. BAY 1125976, a selective allosteric AKT1/2 inhibitor exhibits high efficacy on AKT signaling-dependent tumor growth in mouse models[J]. International Journal of Cancer, 2016, 140(2):449-459.