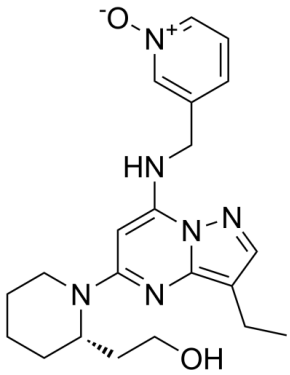
Data Sheet

Product Name:	Dinaciclib
Cat. No.:	CS-0541
CAS No.:	779353-01-4
Molecular Formula:	$C_{21}H_{28}N_6O_2$
Molecular Weight:	396.49
Target:	Apoptosis; CDK
Pathway:	Apoptosis; Cell Cycle/DNA Damage
Solubility:	DMSO : 50 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

Dinaciclib (SCH 727965) is a potent inhibitor of **CDK**, with **IC_{50}**s of 1 nM, 1 nM, 3 nM, and 4 nM for **CDK2**, **CDK5**, **CDK1**, and **CDK9**, respectively[1]. IC50 & Target: IC50: 1 nM (CDK2), 1 nM(CDK5), 3 nM(CDK1), 4 nM(CDK9)[1] ***In Vitro:*** Dinaciclib (SCH 727965) is a potent DNA replication inhibitor that blocks thymidine (dThd) DNA incorporation in A2780 cells with an IC_{50} of 4 nM. Dinaciclib (100 nM) inhibits phosphorylation of the retinoblastoma (Rb) tumor suppressor protein and induces accumulation of the p85 PARP caspase cleavage product[1]. In vitro cell growth of pancreatic cancer cells is inhibited by Dinaciclib (SCH727965) in a dose-dependent manner. Upon incubation with Dinaciclib for 72 h, the GI50s are approximately 10 and 20 nM for MIAPaCa-2 and Pa20C cells, respectively. These results are consistent with studies of Dinaciclib in other cancer cell lines. In soft agar assays, 5 to 10 nM of Dinaciclib significantly reduces colony formation and anchorage independent growth of MIAPaCa-2 cells. Moreover, in vitro cell migration of Pa20C and MIAPaCa-2 cells is significantly reduced by Dinaciclib-concentrations starting from 2-5 nM, as demonstrated using BD FluoroChrom, modified Boyden Chamber and wound healing assays[2]. ***In Vivo:*** Dinaciclib (8, 16, 32, and 48 mg/kg, i.p.) results in tumor inhibition by 70%, 70%, 89%, and 96%, respectively; Dinaciclib (SCH 727965) is well tolerated, and the maximum body weight loss in the highest dosage group is 5%. Dinaciclib has a short plasma half-life in mouse. A dose of 5 mg/kg Dinaciclib given i.p. in mice is associated with a plasma half-life of ~0.25 hour[1]. Treatment with Dinaciclib (SCH727965) given as twice weekly i.p. doses of 40 mg/kg for 4 weeks causes significant tumor growth inhibition (TGI) in 10/10 (100%) of low-passage subcutaneous pancreatic xenografts tested[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]Recombinant cyclin/CDK holoenzymes are purified from Sf9 cells engineered to produce baculoviruses that express a specific cyclin or CDK. Cyclin/CDK complexes are typically diluted to a final concentration of 50 μg/mL in a kinase reaction buffer containing 50 mM Tris-HCl (pH 8.0), 10 mM $MgCl_2$, 1 mM DTT, and 0.1 mM sodium orthovanadate. For each kinase reaction, 1 μg of enzyme and 20 μL of a 2 μM substrate solution (a biotinylated peptide derived from histone H1) are mixed and combined with 10 μL of diluted Dinaciclib (SCH 727965). The reaction is started by the addition of 50 μL of 2 μM ATP and 0.1 μCi of ^{33}P-ATP. Kinase reactions are incubated for 1 hour at room temperature and are stopped by the addition of 0.1% Triton X-100, 1 mM ATP, 5 mM EDTA, and 5 mg/mL streptavidin-coated SPA beads. SPA beads are captured using a 96-well GF/B filter plate and a Filtermate universal harvester. Beads are washed twice with 2 M NaCl and twice with 2 M NaCl containing 1% phosphoric acid. The signal is then assayed using a TopCount 96-well liquid scintillation counter. Dose-response curves are generated from duplicate, eight-point serial dilutions of inhibitory compounds. IC_{50} values are derived by nonlinear regression analysis[1]. **Cell Assay:** Dinaciclib (SCH 727965) is dissolved in DMSO and stored, and then diluted with appropriate media before use[1].[1]A2780 cells are plated onto tissue culture dishes and propagated with the appropriate growth media. Growing cultures are exposed to increasing concentrations of

Dinaciclib (0.75, 1.5, 3.15, 6.25, 12.5, 25, and 500 nM) or a vehicle control, typically for 7 days. After removing the medium, cells are fixed with 50% methanol/50% acetone for 5 minutes and stained with 0.2% crystal violet in 2% ethanol for 5 minutes. Following staining, cells are washed with 5 to 10 mL of water. Stained cells are solubilized in 1% deoxycholic acid, and the absorbance of the resulting solution is measured at 600 nm using a SOFTmax PRO 4.3 plate reader. Absorbance of Dinaciclib-treated samples is plotted as a percent of that of a vehicle-treated control, and data are reported as an IC_{50} value relative to these controls. For suspension cell lines, assessments of cell viability are obtained using the alamarBlue Cell Viability Assay kit[1]. **Animal Administration:** Dinaciclib (SCH 727965) is prepared in 20% hydroxypropyl-β-cyclodextran (Mice)[1][1]Mice[1]
For tumor implantation, specific cell lines are grown in vitro, washed once with PBS, and resuspended in 50% Matrigel in PBS to a final concentration of 4×10^7 to 5×10^7 cells per milliliter. Nude mice are injected with 0.1 mL of this suspension s.c. in the flank region. Tumor length (L), width (W), and height (H) are measured by a caliper twice weekly on each mouse and then used to calculate tumor volume using the formula (L×W×H)/2. When the tumor volume reaches 100 mm^3, the animals are randomized to treatment groups (10 mice/group) and treated i.p. with either Dinaciclib (8, 16, 32, and 48 mg/kg daily, i.p.) or individual chemotherapeutic agents according to the dosing schedule indicated in table and figure legends. Tumor volumes and body weights are measured during and after the treatment periods.

References:

[1]. Parry D, et al. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther. 2010 Aug;9(8):2344-53.

[2]. Feldmann G, et al. Cyclin-dependent kinase inhibitor Dinaciclib (SCH727965) inhibits pancreatic cancer growth and progression in murine xenograft models. Cancer Biol Ther. 2011 Oct 1;12(7):598-609.

CAIndexNames:

2-Piperidineethanol, 1-[3-ethyl-7-[[(1-oxido-3-pyridinyl)methyl]amino]pyrazolo[1,5-a]pyrimidin-5-yl]-, (2S)-

SMILES:

OCC[C@H]1N(CCCC1)C2=NC3=C(C=NN3C(NCC4=C[N+]([O-])=CC=C4)=C2)CC

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