PHA-680632

Cat. No.: HY-10178

CAS No.: 398493-79-3

Molecular Formula: $C_{28}H_{35}N_7O_2$

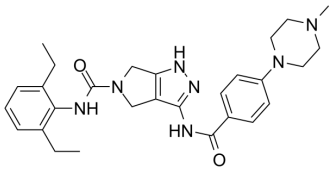
Molecular Weight: 501.62

Target: Aurora Kinase

Pathway: Cell Cycle/DNA Damage; Epigenetics

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 30 mg/mL (59.81 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9935 mL	9.9677 mL	19.9354 mL
5 mM	0.3987 mL	1.9935 mL	3.9871 mL
10 mM	0.1994 mL	0.9968 mL	1.9935 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.15 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.15 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.15 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PHA-680632 is an aurora kinase inhibitor with IC_{50}s of 27, 135 and 120 nM for aurora A, B and C, respectively.

IC_{50} & Target

Aurora A	Aurora B	Aurora C
27 nM (IC_{50})	135 nM (IC_{50})	120 nM (IC_{50})

In Vitro

PHA-680632 shows 30- to 200-fold higher IC_{50}s of FLT3, LCK, PLK1, STLK2, VEGFR2, and VEGFR3 compared with Aurora A.

	PHA-680632 has potent antiproliferative activity in a wide range of cell types. The IC_{50}s are 0.32, 0.41, 0.06, 1.17, 0.56, 0.62, 0.29, 0.11, 1.56, 0.62, 0.07, 0.13, 0.41 μM for C33A, HeLa, HCT116, HT29, LOVO, A549, MCF7, A2780, U2OS, DU145, U937, HL60, NHDF. PHA-680632 can cause polyploidy in tumor cells. PHA-680632 cell treatment induces phenotypes similar to Aurora A or B depletion[1]. PHA680632, inhibits colony formation in different cancer cell lines and induced polyploidy. Aurora-A inhibition by PHA680632 enhances radiation response in cancer cells, especially in p53-deficient cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PHA-680632 suppresses tumor growth in animal models. PHA-680632 treatment at 45 mg/kg dose results in 85% of TGI without signs of toxicity in the HL60 human acute myelogenous leukemia xenograft model. PHA-680632 treatment at 60 mg/kg i.v. b.i.d. for 5 days results in 78% of TGI without signs of toxicity in the A2780 human ovarian carcinoma model[1]. PHA680632 in association with radiation leads to an additive effect in cancer cells, especially in the p53-deficient cells, but does not act as a radiosensitiser[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Inhibition of kinase activity by PHA-680632 is assessed using a scintillation proximity assay format. In this assay, the biotinylated substrate is transphosphorylated by the kinase in presence of ATP traced with γ^{33}-ATP. The phosphorylated substrate is then captured using streptavidin-coated scintillation proximity assay beads and the extent of phosphorylation is evaluated by β-counter after a 4-hour rest for the floatation of the beads on a dense 5 M CsCl solution. In particular a peptide derived from the Chocktide sequence (LRRWSLGL) is used as substrate for Aurora A, whereas the optimized peptide Auroratide1 is employed for Aurora B and C. The assay is run in a robotized format on 96-well plates. The potency of the compound toward Aurora kinases and 29 additional kinases belonging to our Kinase Selectivity Screening panel is evaluated and the relevant IC_{50}s are determined[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cells are seeded at different densities ranging from 5,000 to 15,000 cm^2 in 24-well plate with the appropriate complete medium. After 24 hours, plates are treated with PHA-680632 and incubated for 72 hours at 37°C in 5% CO_2 atmosphere. At the end of incubation time, cells are detached from each plate and counted using a cell counter. IC_{50}s are calculated using percentage of growth versus untreated control[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice: Tumour xenograft mice are randomly allocated into four groups (six mice per group): A, control; B, IR alone, 8 Gy in 1 day; C, PHA-680632 alone, 40 mg/kg, b.i.d., for 4 days; D, same dose of PHA-680632 combined with IR (24 h after the first administration of PHA680632, similar schedule as IR alone) for 4 days. Drug or vehicle control (same volume of 20% Tween-80 in 5% glucose solution) is administered intraperitoneally (i.p.). The tumour size is measured twice a week using an electronic caliper. Follow-up of individual mice is conducted. The tumour volume is estimated from 2D tumour measurements[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Soncini C, et al. PHA-680632, a novel Aurora kinase inhibitor with potent antitumoral activity. Clin Cancer Res. 2006 Jul 1;12(13):4080-9.

[2]. Tao Y, et al. Enhancement of radiation response by inhibition of Aurora-A kinase using siRNA or a selective Aurora kinase inhibitor PHA680632 in p53-deficient cancer cells. Br J Cancer. 2007 Dec 17;97(12):1664-72.

Caution: Product has not been fully validated for medical applications. For research use only.

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