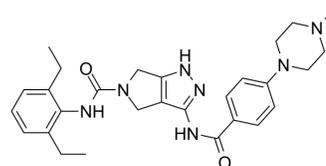


## PHA-680632

|                           |   |       |         |
|---------------------------|---|-------|---------|
| <b>Cat. No.:</b>          | HY-10178  |       |         |
| <b>CAS No.:</b>           | 398493-79-3   |       |         |
| <b>Molecular Formula:</b> | C <sub>28</sub> H <sub>35</sub> N <sub>7</sub> O <sub>2</sub> |       |         |
| <b>Molecular Weight:</b>  | 501.62  |       |         |
| <b>Target:</b>            | Aurora Kinase   |       |         |
| <b>Pathway:</b>           | Cell Cycle/DNA Damage; Epigenetics                            |       |         |
| <b>Storage:</b>           | 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.

|                              | Solvent<br>Concentration | Mass      |           |            |
|------------------------------|--------------------------|-----------|-----------|------------|
|                              |                          | 1 mg      | 5 mg      | 10 mg      |
| Preparing<br>Stock Solutions | 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

- 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
- 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
- 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<sub>50</sub>s of 27, 135 and 120 nM for aurora A, B and C, respectively.

#### IC<sub>50</sub> & Target

|                                       |  |  |
|---------------------------------------|--|--|
| Aurora A<br>27 nM (IC <sub>50</sub> ) | Aurora B<br>135 nM (IC <sub>50</sub> ) | Aurora C<br>120 nM (IC <sub>50</sub> ) |
|---------------------------------------|--|--|

#### In Vitro

PHA-680632 shows 30- to 200-fold higher IC<sub>50</sub>s of FLT3, LCK, PLK1, STK2, VEGFR2, and VEGFR3 compared with Aurora A.

PHA-680632 has potent antiproliferative activity in a wide range of cell types. The IC<sub>50</sub>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<sup>[1]</sup>. 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<sup>[2]</sup>. 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<sup>[1]</sup>. 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<sup>[2]</sup>. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## PROTOCOL

#### Kinase Assay <sup>[1]</sup>

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  $\gamma^{33}$ -ATP. The phosphorylated substrate is then captured using streptavidin-coated scintillation proximity assay beads and the extent of phosphorylation is evaluated by  $\beta$ -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<sub>50</sub>s are determined<sup>[1]</sup>.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### Cell Assay <sup>[1]</sup>

Cells are seeded at different densities ranging from 5,000 to 15,000 cm<sup>2</sup> 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<sub>2</sub> atmosphere. At the end of incubation time, cells are detached from each plate and counted using a cell counter. IC<sub>50</sub>s are calculated using percentage of growth versus untreated control<sup>[1]</sup>.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### Animal Administration <sup>[2]</sup>

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<sup>[2]</sup>.

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.

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

Tel: 609-228-6898

Fax: 609-228-5909

E-mail: [tech@MedChemExpress.com](mailto:tech@MedChemExpress.com)

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA