

Product Data Sheet

Product Name: PND-1186

Cat. No.: GC15164

Chemical Properties

Cas. No. 1061353-68-1

Chemical Name 2-((2-((2-methoxy-4-morpholinophenyl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)-N-methylbenzamide

SMILES CNC(C1=C(NC2=CC(NC3=CC=C(N4CCOCC4)C=C3OC)=NC=C2C(F)(F)F)C=CC=C1)=O

Formula $C_{25}H_{26}F_3N_5O_3$

M.Wt 501.5

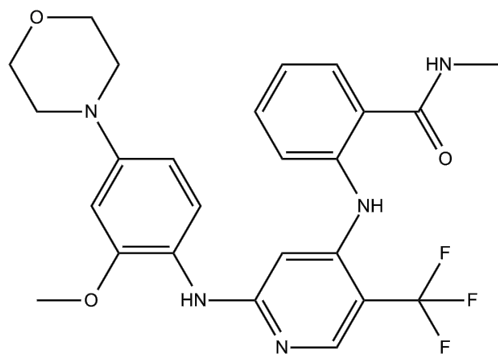
Solubility ≥ 50.2 mg/mL in DMSO

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1,2]:

Cell lines Murine breast carcinoma 4T1, ID8 ovarian carcinoma, human MD-MBA-231 and HEY ovarian cancer cell lines

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Preparation method The solubility of this compound in DMSO is >25.1 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition 0.1 to 1 μ M

Applications In murine breast carcinoma 4T1 cells, ID8 ovarian carcinoma cells and human MD-MBA-231 cells, PND-1186 could inhibit FAK Tyr-397 phosphorylation and increase the protein level of FAK. Meanwhile, PND-1186 could also significantly induce the cell apoptosis and increase the cleavage caspase 3 in suspended but not adherent 4T1 cells. Additionally, PND-1186 was able to promote HEY and OVCAR8 G0/G1 cell cycle arrest followed by cell death whereas growth of SKOV3-IP and OVCAR10 cells were resistant to 1.0 μ M PND-1186.

Animal experiment [3]:

Animal models Mouse xenograft model with 4T1 tumor

Dosage form 150 mg/kg, i.p.

Application Oral administration of 150 mg/kg PND-1186 gave a more sustained PK profile verses i.p., and when given twice daily, PND-1186 significantly inhibited syngeneic murine 4T1 orthotopic breast carcinoma tumor growth and spontaneous metastasis to lungs. Moreover, low-level 0.5 mg/ml PND-1186 ad libitum administration in drinking water prevented oncogenic KRAS- and BRAF-stimulated MDA-MB-231 breast carcinoma tumor growth and metastasis with inhibition of tumoral FAK and p130Cas phosphorylation.

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Other notes Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

- 1.Tanjoni I, Walsh C, Uryu S, et al. PND-1186 FAK inhibitor selectively promotes tumor cell apoptosis in three-dimensional environments. Cancer biology & therapy, 2010, 9(10): 764-777.
- 2.Tancioni I, Uryu S, Sulzmaier F J, et al. FAK inhibition disrupts a beta5 integrin signaling axis controlling anchorage-independent ovarian carcinoma growth. Molecular Cancer Therapeutics, 2014: molcanther. 1063.2014.
- 3.Walsh C, Tanjoni I, Uryu S, et al. Oral delivery of PND-1186 FAK inhibitor decreases tumor growth and spontaneous breast to lung metastasis in pre-clinical models. Cancer biology & therapy, 2010, 9(10): 778.

Background

PND-1186 is a reversible inhibitor of FAK (focal adhesion kinase) with IC50 value of 1.5 nM [1]. The cytoplasmic protein-tyrosine kinase FAK is associated with integrins and growth factor receptors. It modulates a variety of cellular processes when it is activated. Since the elevated expression of FAK is found in many tumors, the inhibitors of FAK are developed as anti-tumor drugs in cancer therapy. PND-1186 is one of these ATP-competitive small-molecule inhibitors. It inhibited the autophosphorylation of FAK tyrosine-397 with IC50 value of 0.1 μ M in breast carcinoma cells. When the concentration was up to 1 μ M, PND-1186 also inhibited more than 50% of the activities of other kinases, such as CDK2, Lck, Aurora-A and ACK1 [1].

PND-1186 at concentrations of 0.1 to 1 μ M inhibited the phosphorylation of FAK Tyr-397 and increased the protein level of FAK in murine breast carcinoma 4T1 cells, ID8 ovarian carcinoma cells and human MD-MBA-231 cells. Meanwhile, PND-1186 significantly induced cell apoptosis and increased the cleavage caspase 3 in suspended but not adherent 4T1 cells. Besides that, PND-1186 is found to inhibit the movement of 4T1 cells in both the wound healing assays and the millicell chamber motility assays. Treatment of PND-1186 at 0.4 μ M for 4 hours showed the maximal inhibition of about 60%. In HEY ovarian cancer cells, treatment of PND-1186 caused the decrease of

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pY397 FAK, $\beta 5$ integrin and osteopontin. It also induced cell cycle arrest at G0-G1 phase [1, 2]. In subcutaneous 4T1 tumors, administration of PND-1186 at dose of 100 mg/kg caused inhibition of both FAK Tyr-397 phosphorylation and p130Cas Tyr-410 phosphorylation. In orthotopic 4T1 tumors, administration of 150 mg/kg PND-1186 for 16 days finally reduced 3.1-fold tumor volume. Moreover, PND-1186 is reported to have anti-inflammatory effects and can suppress the processes of spontaneous breast cancer metastasis to lung [3].

References:

1. Tanjoni I, Walsh C, Uryu S, et al. PND-1186 FAK inhibitor selectively promotes tumor cell apoptosis in three-dimensional environments. *Cancer biology & therapy*, 2010, 9(10): 764-777.
2. Tancioni I, Uryu S, Sulzmaier F J, et al. FAK inhibition disrupts a beta5 integrin signaling axis controlling anchorage-independent ovarian carcinoma growth. *Molecular Cancer Therapeutics*, 2014: molcanther. 1063.2014.
3. Walsh C, Tanjoni I, Uryu S, et al. Oral delivery of PND-1186 FAK inhibitor decreases tumor growth and spontaneous breast to lung metastasis in pre-clinical models. *Cancer biology & therapy*, 2010, 9(10): 778.

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