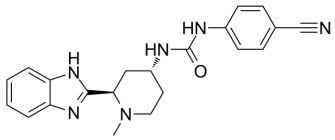
Glasdegib

Cat. No.:	HY-16391
CAS No.:	1095173-27-5
Molecular Formula:	$C_{21}H_{22}N_6O$
Molecular Weight:	374.44
Target:	Smo
Pathway:	Stem Cell/Wnt
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 : 62.5 mg/mL (166.92 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6707 mL	13.3533 mL	26.7066 mL
5 mM	0.5341 mL	2.6707 mL	5.3413 mL
10 mM	0.2671 mL	1.3353 mL	2.6707 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 (5.55 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.55 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.55 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Glasdegib (PF-04449913) is a potent and orally bioavailable smoothened inhibitor. Glasdegib (PF-04449913) binds to human SMO (amino acids 181-787) with an IC_{50} of 4 nM[1].

IC_{50} & Target

IC50: 4 nM (Smo)[1]

In Vitro

Glasdegib (PF-04449913) inhibits sonic hedgehog (Shh) stimulated luciferase expression in mouse embryonic fibroblasts with an IC_{50} of 6.8 nM; and significantly reduces medulloblastoma growth in a $Ptch1^{+/-}p53^{+/-}$ allograft model at doses that

	decreased murine Shh target gene expression. In stromal co-culture experiments, FACS analysis demonstrates a significant reduction in BC LSC by Glasdegib (PF-04449913) when compared with normal progenitors. Importantly, human BC LSC engrafted RAG2$^{-/-}\gamma_C^{-/-}$ mice treated daily with Glasdegib (PF-04449913) compared with vehicle treated controls have a significant spleen weight reduction (p=0.006). This reduction in leukemic burden corresponded with decreased GLI2 protein expression, as determined by both nanoproteomic analysis of FACS purified human progenitors and GLI2 confocal fluorescence microscopic analysis of splenic sections[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Human BC LSC engrafted RAG2$^{-/-}\gamma_C^{-/-}$ mice treated daily with Glasdegib (PF-04449913) compared with vehicle treated controls had a significant spleen weight reduction (p=0.006). When CD34$^+$ cord blood engrafted NSG mice are treated with Glasdegib (PF-04449913), the frequency of human CD45$^+$ cells, progenitors and both myeloid and lymphoid cell fate commitment remained comparable to vehicle treated controls indicating that unlike LSC, normal human HSC cell fate decisions are Hh pathway independent. These results highlight the important niche dependent effects of selective SMO inhibition that induce GLI2 downregulation in a cell type and context specific manner[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Normal or BC CML CD34$^+$ cells are treated with vehicle, Glasdegib (PF-04449913) (1 μM), BMS-354825 (50 nM), or combination treatment. Mouse bone marrow stromal cell lines, M2-10B4 (M2) and SL/SL (SL) are plated in a 1:1 mixture at a total concentration of 100,000 cells/mL one day prior to co-culture with 10,000-20,000 CD34$^+$ BC CML or normal progenitors. After 1 week of culture, progenitors are FACS sorted into hematopoietic progenitor assays and colonies are scored at 14 days. To assess survival of normal human hematopoietic stem and progenitor cells, irradiated (20 Gray) OP9 (M2 clone) stromal cells are co-cultured with 50,000 human CD34$^+$ cord blood cells, vehicle or Glasdegib (PF-04449913) in AlphaMEM with 20% Hyclone FBS, 1% pen strep glutamine and supplemented with 50 ng/mL SCF, 10 ng/mL thrombopoietin, and 10 ng/mL Flt3 and quantified by weekly FACS analysis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] RAG2$^{-/-}$c$^{-/-}$ mice are transplanted intrahepatically with equal numbers of normal progenitors or BC LSC. Upon detection of human CD45$^+$ cell peripheral blood engraftment, mice are treated daily by oral gavage with vehicle (50% 1,2 Propandiol, 50% HBSS or methylcellulose), Glasdegib (100 mg/kg), BMS-354825 (50 mg/kg), or the combination for 14 days followed by FACS to quantify human engraftment in hematopoietic niches. To assess effects on normal HSC function, 7 to 10 week old NOD. Cg-PrkdcSCID IL2R1Wjl/SzJ mice are sublethally irradiated, transplanted retro-orbitally with 100,000 CD34$^+$ human cord blood cells and treated 8 weeks later with vehicle or Glasdegib (100 mg/kg) for 14 days followed by FACS engraftment analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Arab J Chem. 2023 Jul 4, 105117.
- Molecules. 2023 Mar 4.
- Univerzita Karlova v Praz. 2021 Jul.
- Methods Mol Biol. 2018;1711:351-398.

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REFERENCES

[1]. Sadarangani A, et al. GLI2 inhibition abrogates human leukemia stem cell dormancy. J Transl Med. 2015 Mar 21;13:98.

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