Product Data Sheet

Product Name: SNX-5422 Mesylate (PF-04929113 (Mesylate))
Cat. No.: GC33047

Chemical Properties

Cas. No.	1173111-67-5		
SMILES	CS(=O)(O)=O.O=C1CC(C)(C)CC2=C1C(C(F)(F)F)=NN2C3=CC=C(C(N[C@@H]4CC[C@@H](OC(CN)=O)CC4)=C3)C(N)=O		
Formula	$C_{26}H_{34}F_3N_5O_7S$	M.Wt	617.64
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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

Kinase experiment:

Briefly, Hsp90 from porcine spleen extract is isolated by affinity capture on a purine-affinity media. The Hsp90 loaded media is then challenged with test compound (SNX-5422) at a given concentration, ranging from 0.8 to 500 μM, and the amount of Hsp90 liberated at each concentration is determined. The resulting IC50 values are corrected for the ATP ligand concentration and presented as apparent Kd values[1].

Cell experiment:

Cell viability is determined by the CCK-8 Assay Kit. Cells (5 × 103/100 μL) in each well on 96-well plates are incubated overnight, and treated with the drugs (SNX-5422) for an additional 4 h at 37°C. Absorbance is measured at 450 nm using a spectrophotometer. All experiments are performed in triplicate[3].

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Animal experiment:

Female nude mice are 11 to 12 weeks old and have a body weight range of 18.7−30.5 g on Day 1 of the study. Xenografts are initiated from HT-29 human colon carcinoma tumors maintained by serial transplantation in athymic nude mice. Each test mouse receives a 1 mm3 HT-29 tumor fragment implanted subcutaneously in the right flank, and the growth of tumors is monitored as the average size approached 80−120 mm3. Fourteen days later, designated as Day 1 of the study, individual tumor volumes range from 63 to 126 mm3 and the animals are placed into eight groups, each consisting of 10 mice with group mean tumor volumes of 93.2−93.9 mm3. Micronized SNX-5422 is preformulated in 1% microcrystalline cellulose/0.5% Tween80 in water. The solutions are stored at 4°C during the study and homogenized just prior to dosing. Group 1 vehicle control mice receive D5W (5% dextrose) vehicle by oral gavage beginning on Day 1, every other day for three doses, followed by two days without treatment, for three cycles ((qod × 3)/2 × 3 weeks, total of nine doses). Groups 2 to 5 animals receive 10 at 5, 10, 25, or 50 mg/kg on the same schedule as vehicle control group ((qod × 3)/2 × 3). Each treatment is administered in a volume of 0.2 mL per 20 g of body weight (10 mL/kg) and is scaled to the body weight of the animal. Tumors are measured twice weekly using calipers[1].

References:

[1]. Huang KH, et al. Discovery of novel 2-aminobenzamide inhibitors of heat shock protein 90 as potent, selective and orally active antitumor

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agents. J Med Chem. 2009 Jul 23;52(14):4288-305
[2]. Chandarlapaty S, et al. SNX2112, a synthetic heat shock protein 90 inhibitor, has potent antitumor activity against HER kinase-dependent cancers. Clin Cancer Res. 2008 Jan 1;14(1):240-8.
[3]. Kim SH, et al. The heat shock protein 90 inhibitor SNX5422 has a synergistic activity with histone deacetylase inhibitors in induction of death of anaplastic thyroid carcinoma cells. Endocrine. 2016 Feb;51(2):274-

82.

Background

PF-04929113 is a prodrug for the Hsp90 inhibitor, PF-04928473 , which binds both Hsp90α and Hsp90β with an IC_{50} value of 30 nM.[1,2] The prodrug, PF-04929113, is rapidly absorbed and converted into the active inhibitor after oral administration.[2] The active inhibitor causes degradation of Hsp90 client proteins, including HER2, and reduces phosphorylation of downstream kinases, including Akt and ERK1/2, leading to apoptosis in cancer cells.[1,3] Oral administration of the prodrug, PF-04929113, reduces tumor growth and prolongs survival in mouse models of multiple myeloma and prostate cancer.[3,4]

1.Chandarlapaty, S., Sawai, A., Ye, Q., et al.SNX2112, a synthetic heat shock protein 90 inhibitor, has potent antitumor activity against HER kinase-dependent cancersClin. Cancer Res.14(1)240-248(2008) 2.Jain, L., Gardner, E.R., Venitz, J., et al.Determination of PF-04928473 in human plasma using liquid chromatography with tandem mass spectrometryJ. Chromatogr. B Analyt. Technol. Biomed. Life Sci.878(30)3187-3192(2010) 3.Okawa, Y., Hideshima, T., Steed, P., et al.SNX-2112, a selective Hsp90 inhibitor, potently inhibits tumor cell growth, angiogenesis, and osteoclastogenesis in multiple myeloma and other hematologic tumors by abrogating signaling via Akt and ERKBlood113(4)846-855(2009) 4.Lamoureux, F., Thomas, C., Yin, M.J., et al.A novel HSP90 inhibitor delays castrate-resistant prostate cancer without altering serum PSA levels and inhibits osteoclastogenesisClin. Cancer Res.17(8)2301-2313(2011)

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