Product Data Sheet

Product Name: Senexin B
Cat. No.: GC19326

Chemical Properties

Cas. No.	1449228-40-3		
SMILES	N#CC1=CC2=C(NCCC3=CC=C4C=C(C(N5CCN(C)CC5)=O)C=CC4=C3)N=CN=C2C=C1		
Formula	$C_{27}H_{26}N_6O$	M.Wt	450.53
Solubility	DMSO : 6 mg/mL (13.32 mM)	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	Senexin B		

Protocol

Animal experiment:

Mice: Once tumors reach 100-200 mm3 volume, 4 groups of mice are treated with vehicle, Senexin B dimaleate (100 mg/kg; twice daily, oral gavage in 6.25% 2-Hydroxypropyl-β-cyclodextrin, 1% Dextrose buffer) alone or in combination with fulvestrant (5 mg/mouse; s.c; once/week). Tumor volumes are measured twice weekly with calipers and volumes are calculated. After 40 days mice are euthanized, tumors are excised and weighed[2].

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References:

[1]. Porter D, et al. Abstract PR08: Targeting tumor microenvironment with selective small-molecule inhibitors of CDK8/19. Abstracts: AACR Special Conference on Cellular Heterogeneity in the Tumor Microenvironment; 2014 Feb 26-Mar 1; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2015;75(1 Suppl):Abstract nr PR08. doi:10.1158/1538-7445.CHTME14-PR08
[2]. McDermott MS, et al. Inhibition of CDK8 mediator kinase suppresses estrogen dependent transcription and the growth of estrogen receptor positive breast cancer. Oncotarget. 2017 Feb 21;8(8):12558-12575.
[3]. CDK8-CDK19 selective inhibitors and their use in anti-metastatic and chemopreventative methods for cancer. US 9321737 B2

Background

Senexin B is a potent, highly water-soluble and bioavailable CDK8/19 inhibitor, with Kds of 140 nM for CDK8 and 80 nM for CDK19.

Senexin B inhibits CDK8/19 in low nanomolar range[1]. Senexin B is a newly optimized derivative of Senexin A. It has the same high selectivity for CDK8/19 and is more potent than Senexin A. Senexin B strongly reduces the emergence of estrogen independent cells. Senexin B shows synergy with fulvestrant in MCF7, T47D-ER/Luc and BT474[2].

Pretreatment of tumor-free mice with Senexin B significantly inhibits the growth of triple-negative breast cancer (TNBC) cells inoculated into mice subsequently to Senexin B administration, indicating a general chemopreventive effect on the normal tissue "soil". Senexin B potentiates the tumor-suppressive effect of doxorubicin on established TNBC xenografts; this effect is associated with the suppression of NFκB-mediated transcriptional induction of tumor-promoting cytokines. Senexin B inhibits invasive growth into the muscle layer in an orthotopic xenograft model of MDA-MB-468 TNBC cells. In a spleen-to-liver colon cancer metastasis model of syngeneic mouse CT26

tumors, Senexin B treatment of mice have the same effect as CDK8 knockdown in tumor cells: suppression of metastatic growth in the liver without a significant effect on primary tumor growth in the spleen[1]. Senexin B suppresses tumor growth and augmentes the effects of fulvestrant in ER-positive breast cancer xenografts[2].

References:

[1]. Porter D, et al. Abstract PR08: Targeting tumor microenvironment with selective small-molecule inhibitors of CDK8/19. Abstracts: AACR Special Conference on Cellular Heterogeneity in the Tumor Microenvironment; 2014 Feb 26-Mar 1; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2015;75(1 Suppl):Abstract nr PR08. doi:10.1158/1538-7445.CHTME14-PR08
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