Product Data Sheet

Product Name: R406
Cat. No.: GC16796

Chemical Properties

Cas. No.	841290-81-1		
Chemical Name	benzenesulfonic acid;6-[[5-fluoro-2-(3,4,5-trimethoxyanilino)pyrimidin-4-yl]amino]-2,2-dimethyl-4H-pyrido[3,2-b][1,4]oxazin-3-one		
SMILES	CC1(C(=O)NC2=C(O1)C=CC(=N2)NC3=NC(=NC=C3F)NC4=CC(=C(C(=C4)OC)OC)OC)C.C1=CC=C(C=C1)S(=O)(=O)O		
Formula	$C_{22}H_{23}FN_6O_5.C_6H_6O_3S$	M.Wt	628.63
Solubility	≥ 31.45mg/mL 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	R406		

Protocol

Cell experiment [1]:

Cell lines	Human diploid fibroblasts
Preparation Method	Cells were seeded in the 24-well plate and respectively treated with 1, 2, 5, 10 and 20μM of R406 for 24 hours in the growth media.
Reaction Conditions	1, 2, 5, 10, 20μM; 24h
Applications	R406 induced apoptotic cell death by inhibiting FAK and p38 activity as well as increasing ROS.

Animal experiment [2]:

Animal models	Male Wistar rats
Preparation Method	Rats were randomized into Normal, diabetic mellitus (DM), DM with 5mg/kg R406 and DM with 10mg/kg R406 groups. DM rats were established via injection of streptozotocin (STZ). One week after model establishment, rats in treatment groups received 5mg/kg or 10mg/kg R406 by gavage administration for 12 weeks consecutively.

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Dosage form	5 or 10mg/kg; gavage administration; daily for 12 weeks.
Applications	R406 could ameliorate STZ induced pericyte loss, acellular capillary formation and retinal vascular leakage; exerted protective effect on blood–retinal barrier; attenuate retinal cell apoptosis; and enhanced retinal cell proliferation.

References:
[1] Cho H J, Yang E J, Park J T, et al. Identification of SYK inhibitor, R406 as a novel senolytic agent. Aging (Albany NY). 2020 May 7;12(9):8221-8240.
[2] Su X, Sun Z H, Ren Q, et al. The effect of spleen tyrosine kinase inhibitor R406 on diabetic retinopathy in experimental diabetic rats. Int Ophthalmol. 2020 Sep;40(9):2371-2383.

Background

R406 is an orally available spleen tyrosine kinase (Syk) inhibitor with an IC_{50} value of 41nM and competitive inhibitor for ATP binding with a K_i of 30nM[1]. R406 also inhibits the isolated enzymes Lyn with IC_{50} value of 63nM and Lck with IC_{50} value of 37nM. Despite similar IC_{50} values on isolated kinases, R406 shows selectivity in cell-based assays[2].

In vitro, human diploid fibroblasts were treated with 1, 2, 5, 10 and 20μM of R406 for 24 hours in the growth media. R406 induced apoptotic cell death by inhibiting FAK and p38 activity as well as increasing ROS[3]. Two patient-derived glioma stem cell (GSC) lines, GSC-1 (Syk-positive) and GSC-2 (Syk-negative), were treated with 0.75–0.89μM R406 for 72h. R406 significantly inhibited neurosphere formation and triggered apoptosis in GSCs. R406 also induced a metabolic shift from glycolysis to oxidative phosphorylation (OXPHOS) and subsequently production of excess ROS in GSCs[4]. PBMC or purified T cells from chronic lymphocytic leukemia (CLL) patients were pretreated with R406 (0.1 or 1μM) for 30min and then activation markers, cell proliferation and chemotaxis assay were evaluated. R406 impaired the expression of activation markers and cytokine-secretion in response to TCR/CD3 stimulation on T cells. R406 also impaired T cell proliferation in response to TCR/CD3 and IL-15 stimulation and T cell migration in response to CCL21, CCL19 and CXCL12[5].

In vivo, streptozotocin (STZ) induced diabetic mellitus rat models were given with 5 and 10mg/kg/day R406, respectively via gavage administration for 12 consecutive weeks. R406 could ameliorate STZ induced pericyte loss, acellular capillary formation and retinal vascular leakage; exerted protective effect on blood–retinal barrier; attenuated retinal cell apoptosis; and enhanced retinal cell proliferation[6]. Mouse chronic migraine (CM) models were pretreated with R406 (5mg/kg) via intraperitoneal administration. R406 significantly ameliorated pain hypersensitivity in CM mice and decreased the protein levels of both CGRP and c-fos in the vicinity of trigeminal nucleus caudalis. R406 inhibited microglia activation and NLRP3 inflammasome at trigeminal nucleus caudalis sites, accompanied by a down-regulation of mature IL-1β expression[7].

References:
[1] Sylvia Braselmann, Boyle L D, Inoue T, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. J Pharmacol Exp Ther. 2006 Dec;319(3):998-1008.
[2] Hoon-Suk Cha, Taylor V, Zhao H R, et al. A novel spleen tyrosine kinase inhibitor blocks c-Jun N-terminal kinase-

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mediated gene expression in synoviocytes. J Pharmacol Exp Ther. 2006 May;317(2):571-8.
[3] Cho H J, Yang E J, Park J T, et al. Identification of SYK inhibitor, R406 as a novel senolytic agent. Aging (Albany NY). 2020 May 7;12(9):8221-8240.
[4] Sun S X, Xue D D, Chen Z J, et al. R406 elicits anti-Warburg effect via Syk-dependent and -independent mechanisms to trigger apoptosis in glioma stem cells. Cell Death Dis. 2019 May 1;10(5):358.
[5] Colado A, Almejún M B, Podaza E, et al. The kinase inhibitors R406 and GS-9973 impair T cell functions and macrophage-mediated anti-tumor activity of rituximab in chronic lymphocytic leukemia patients. Cancer Immunol Immunother. 2017 Apr;66(4):461-473.
[6] Su X, Sun Z H, Ren Q, et al. The effect of spleen tyrosine kinase inhibitor R406 on diabetic retinopathy in experimental diabetic rats. Int Ophthalmol. 2020 Sep;40(9):2371-2383.
[7] Fan Z Z, Su D D, Li Z C, et al. Metformin attenuates central sensitization by regulating neuroinflammation through the TREM2-SYK signaling pathway in a mouse model of chronic migraine. J Neuroinflammation. 2024 Dec 3;21(1):318.

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