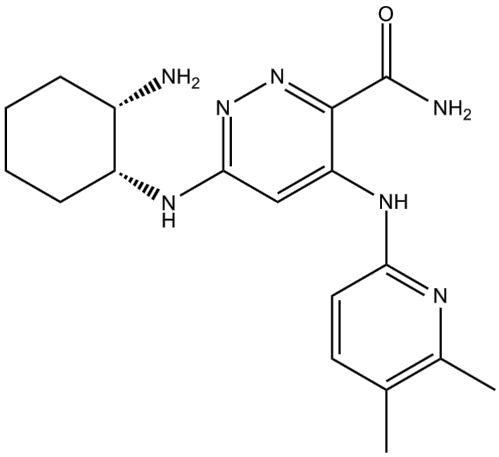
Product Data Sheet

Product Name: RO9021
Cat. No.: GC15466

Chemical Properties

Cas. No.	1446790-62-0		
Chemical Name	6-(((1R,2S)-2-aminocyclohexyl)amino)-4-((5,6-dimethylpyridin-2-yl)amino)pyridazine-3-carboxamide		
SMILES	O=C(C1=NN=C(N[C@H]2[C@@H](N)CCCC2)C=C1NC3=NC(C)=C(C)C=C3)N		
Formula	$C_{18}H_{25}N_7O$	M.Wt	355.44
Solubility	Soluble 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

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Kinase experiment: The inhibitory potency to SYK is determined in a radiometric assay using inactive SYK kinase. Briefly, SYK protein is dephosphorylated by PTP1B phosphatase and then the reaction is initiated by the addition of substrate cocktail that contained 20 μM ATP, 0.025 μCi ATP-γ-33P and 10 μM biotinylated synthetic peptide. The reaction is carried out for 30 minutes and resulting 33P incorporation is determined by top counter.

Animal experiment: Briefly, DBA1/J male mice are injected intradermally with 0.1 mL bovine type II collagen (100 μg) and complete Freund's adjuvant followed by second immunization on day 21 with bovine type II collagen and incomplete Freund adjuvant. RO9021 is administered orally, randomized into different groups (14 mice/groups), every day for 14 days starting on the day after second immunization. Clinical arthritis scores (1 to 4) of individual paws are assessed and the arthritic index for each mouse is determined by adding the individual scores of all four paws. The level of cytokines in serum is determined by Luminex analysis.

References:

[1]. Liao C, et al. Selective inhibition of spleen tyrosine kinase (SYK) with a novel orally bioavailable small molecule inhibitor, RO9021, impinges on various innate and adaptive immune responses: implications for SYK inhibitors in autoimmune disease therapy.

Background

IC50: 5.6 nM

RO9021 is a Syk inhibitor.

Spleen tyrosine kinase (SYK) is identified as a critical integrator of intracellular signals regulated by activated immunoreceptors, such as Fc receptors and Bcell receptors (BCR), which are of great importantance for the function and development of lymphoid cells.

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In vitro: Previous study found that in addition to the suppression of Bcell receptor signaling in human peripheral blood mononuclear cells and whole blood, FcγR signaling in human monocytes, and Fc R signaling in human mast cells, RO9021 could also block the in vitro osteoclastogenesis from mouse bone marrow macrophages. Moreover, the Toll-like Receptor 9 signaling in human Bcells could be blocked by RO9021, leading to the decreased levels of plasmablasts, immunoglobulin (Ig) G and IgM upon B-cell differentiation. In addition, RO9021 could also potently inhibit type I interferon production by human plasmacytoid dendritic cells (pDC) via TLR9 activation, and such effect was found to be specific to TLR9 since RO9021 did not show inhibitary effect on TLR4- or JAK-STAT-mediated signaling [1].

In vivo: Animal study showed that the oral administration of RO9021could significanly inhibit the arthritis progression in the mCIA model, with well observed pharmacokinetics-pharmacodynamic correlation [1].

Clinical trial: Up to now, RO9021 is still in the preclinical development stage.

Reference:
[1] Liao C, et al. Selective inhibition of spleen tyrosine kinase (SYK) with a novel orally bioavailable small molecule inhibitor, RO9021, impinges on various innate and adaptive immune responses: implications for SYK inhibitors in autoimmune disease therapy. Arthritis Res Ther. 2013 Oct 4;15(5):R146.

Caution: Product has not been fully validated for medical applications. For research use only.
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