

产品名称: **Pacritinib**

产品别名: **SB1518**

生物活性:

Description	Pacritinib is a potent inhibitor of both wild-type JAK2 (IC ₅₀ =23 nM) and JAK2 ^{V617F} mutant (IC ₅₀ =19 nM). Pacritinib also inhibits FLT3 (IC ₅₀ =22 nM) and its mutant FLT3 ^{D835Y} (IC ₅₀ =6 nM).					
IC ₅₀ & Target	JAK2 ^{V617F}	JAK2 ^{wt}	Tyk2	JAK3	JAK1	FLT3 ^{D835Y}
	19 nM (IC ₅₀)	23 nM (IC ₅₀)	50 nM (IC ₅₀)	520 nM (IC ₅₀)	1280 nM (IC ₅₀)	6 nM (IC ₅₀)
	FLT3 ^{wt}					
	22 nM (IC ₅₀)					
In Vitro	Relative to JAK2, Pacritinib (SB1518) is two-fold less potent against TYK2 (IC ₅₀ =50 nM), 23-fold less potent against JAK3 (IC ₅₀ =520 nM) and 56-fold less potent against JAK1 (IC ₅₀ =1280 nM). The rest of the evaluated kinases show <30% inhibition when tested against 100 nM Pacritinib at adenosine triphosphate concentrations equivalent to its Michaelis constant (K _m). Pacritinib inhibits MV4-11 and MOLM-13 cells (both of which are cell lines derived from human acute myeloid leukemias driven by an FLT3 ITD mutation) with IC ₅₀ of 47 and 67 nM, respectively. Pacritinib inhibits Karpas 1106P and Ba/F3-JAK2 ^{V617F} cells (which are cell lines dependent on JAK2 signaling) with IC ₅₀ of 348 and 160 nM, respectively[1]. FLT3-ITD harboring MV4-11 cells are treated for 3 h with different concentrations of Pacritinib (SB1518) and pFLT3, pSTAT5 and pERK1/2 levels are quantified. Pacritinib leads to a dose-dependent decrease of pFLT3, pSTAT5, pERK1/2 and pAkt with IC ₅₀ of 80, 40, 33 and 29 nM, respectively. The IC ₅₀ on auto-phosphorylation of FLT3-wt in RS4;11 is four-fold higher (IC ₅₀ =600 nM) compare with FLT3-ITD in MV4-11 and MOLM-13 cells. However, STAT5 inhibition is detected at much lower concentrations of Pacritinib (IC ₅₀ =8 nM) [2].					
In Vivo	For evaluation of efficacy in the Ba/F3-JAK2 ^{V617F} engraftment model, mice are treated with Pacritinib (SB1518) at doses of 50 or 150 mg/kg p.o. q.d. for 13 days, with drug dosing starting 4 days after cell inoculation. At study termination, the vehicle control mice exhibit splenomegaly and hepatomegaly (~7- and 1.3-fold, respectively), reminiscent of the symptoms found in patients with symptomatic myelofibrosis. SB1518 treatment at 150 mg/kg p.o. q.d. significantly ameliorates all these symptoms, with 60% (±9%) normalization of spleen weight and 92% (±5%) normalization of liver weight and is well tolerated without significant weight loss or any hematological toxicities, including thrombocytopenia and anemia[1]. In rats, Pacritinib (SB1518) shows moderately fast absorption (t _{max} =4 h), with a peak concentration of 114 ng/mL, AUC of 599 ng·h/mL, and a terminal half-life of ~6 h following a single oral dose of 10 mg/kg. In dogs, Pacritinib (SB1518) is rapidly absorbed (t _{max} =2.0 h), with a peak concentration of ~12 ng/mL, AUC of 53 ng·h/mL, and a terminal half-life of 3.4 h following a single oral dose of 3 mg/kg[3].					
Solvent&Solubility	In Vitro: DMSO : 5.4 mg/mL (11.43 mM; Need ultrasonic and warming)					
	Preparing Stock Solutions	<div>Solvent / Mass / Concentration</div>	1 mg	5 mg	10 mg	
		1 mM	2.1160 mL	10.5802 mL	21.1604 mL	
		5 mM	0.4232 mL	2.1160 mL	4.2321 mL	
		10 mM	0.2116 mL	1.0580 mL	2.1160 mL	
*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液，一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。						

	<p>储备液的保存方式和期限 -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。</p>
References	<p>[1]. Hart S, et al. SB1518, a novel macrocyclic pyrimidine-based JAK2 inhibitor for the treatment of myeloid and lymphoid malignancies. <i>Leukemia</i>. 2011 Nov;25(11):1751-9.</p> <p>[2]. Hart S, et al. Pacritinib (SB1518), a JAK2/FLT3 inhibitor for the treatment of acute myeloid leukemia. <i>Blood Cancer J</i>. 2011 Nov;1(11):e44.</p> <p>[3]. William AD, et al. Discovery of the macrocycle 11-(2-pyrrolidin-1-yl-ethoxy)-14,19-dioxo-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene (SB1518), a potent Janus kinase 2/fms-like tyrosine kinase-3 (JA</p>
实验参考:	
Cell Assay	<p>SET-2 and Karpas 1106P cells, and Ba/F3-JAK2^{V617F}-GFP-Luc cells are used. For proliferation assays in 96-well plates, cells are seeded at 30-50% confluency and are treated the following day with compounds (e.g., Pacritinib) (in triplicate) at concentrations up to 10 µM for 48 h. Cell viability is monitored using the CellTiter-Glo assay. Dose-response curves are plotted to determine IC₅₀ values for the compounds using the XL-fit software[1]</p>
Animal Administration	<p>Mice[1] Female athymic BALB/c nude mice (BALB/cOlaHsd-Foxn1^{nu}) of age 12 weeks are used; and female SCID Beige mice (CB17.Cg-Prkdc^{scid}Lys^{bg}/CrI) of age 9-10 weeks are used. For the SET-2 leukemia model, 5×10⁶ tumor cells are injected subcutaneously in the right flank of severe combined immunodeficient beige mice. The cells are resuspended in 50 µL serum-free growth medium, mixed 1:1 with Matrigel and injected in a total volume of 100 µL. Tumor volumes are determined by caliper measurements and drug treatment is initiated after 31 days when tumors have reached a mean volume of 280 mm³ (tumor volume (mm³)=(w²×l)/2). This study is performed using 12 mice per group and animals are killed 3 h post-dose on day 18. Tumor growth inhibition is calculated. For the efficacy studies, mice are treated by oral gavage (10 mL/kg body weight) with doses from 50 to 150 mg/kg SB1518.</p> <p>Rats and Dogs[3] Male Wistar rats (aged 6-8 weeks, weighing 270 to 325 g) and male Beagle dogs (6 to 7 months of age, weighing 9-11 kg) are used in this study. The oral doses for dogs and rats are 3, and 10 mg/kg, respectively. The doses are administered, by gavage, as suspensions (0.5 % methylcellulose and 0.1% tween 80) to rats, and as gelatin capsules to dogs. Following oral dosing, serial blood samples are collected (jugular vein in dogs, and superior vena cava in rats) at different time points (0 to 24 h) in tubes containing K₃EDTA as anticoagulant, and centrifuged, the plasma is separated and stored at -70°C until analysis. Plasma samples are processed and analyzed by LC/MS/MS.</p> <p>Pharmacokinetic parameters are estimated by noncompartmental methods using WinNonlin.</p>
Kinase Assay	<p>All assays are carried out in 384-well white microtiter plates. Compounds (e.g., Pacritinib) are 4-fold serially diluted in 8 steps, starting from 10 µM. The reaction mixture consist of 25 µL assay buffer (50 mM HEPES pH 7.5, 10 mM MgCl₂, 5 mM MnCl₂, 1 mM DTT, 0.1 mM Na₃VO₄, 5 mM β-glycerol phosphate). For FLT3 assays, the reaction contain 2.0 µg/mL FLT3 enzyme, 5 µM of poly(Glu,Tyr) substrate and 4 µM of ATP. For JAK1 assays, the reaction contain 2.5 µg/mL of JAK1 enzyme, 10 µM of poly(Glu,Ala,Tyr) substrate and 1.0 µM of ATP. For JAK2 assays, the reaction contain 0.35 µg/mL of JAK2 enzyme, 10 µM of poly (Glu,Ala,Tyr) substrate and 0.15 µM of ATP. For JAK3 assays, the reaction contain 3.5 µg/mL of JAK3 enzyme, 10 µM of poly (Glu,Ala,Tyr) substrate and</p>

	6.0 μ M of ATP. For TYK2 assays, the reaction contain 2.5 μ g/mL of TYK2 enzyme, 10 μ M of poly (Glu,Ala,Tyr) substrate and 0.15 μ M of ATP. The reaction is incubated at room temperature for 2 h prior to addition of 13 μ L PKLight detection reagent. After 10 min incubation luminescent signals are read on a multi-label plate reader[1]
References	<p>[1]. <u>Hart S, et al. SB1518, a novel macrocyclic pyrimidine-based JAK2 inhibitor for the treatment of myeloid and lymphoid malignancies. Leukemia. 2011 Nov;25(11):1751-9.</u></p> <p>[2]. <u>Hart S, et al. Pacritinib (SB1518), a JAK2/FLT3 inhibitor for the treatment of acute myeloid leukemia. Blood Cancer J. 2011 Nov;1(11):e44.</u></p> <p>[3]. <u>William AD, et al. Discovery of the macrocycle 11-(2-pyrrolidin-1-yl-ethoxy)-14,19-dioxo-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene (SB1518), a potent Janus kinase 2/fms-like tyrosine kinase-3 (JA</u></p>



源叶生物