

产品名称: **TG101348 (SAR302503)**

产品别名: **Fedratinib**

**生物活性:**

<b>Description</b>	Fedratinib (TG-101348) is a selective inhibitor of JAK2 with an IC <sub>50</sub> of 3 nM, showing 35- and 334-fold selectivity over JAK1 and JAK3, respectively.			
<b>IC<sub>50</sub> &amp; Target</b>	JAK2	JAK2(V617F)	Flt3	Ret
	3 nM (IC <sub>50</sub> )	3 nM (IC <sub>50</sub> )	15 nM (IC <sub>50</sub> )	48 nM (IC <sub>50</sub> )
<b>In Vitro</b>	<p>Fedratinib (TG-101348) significantly inhibits JAK2 V617F, Flt3, and Ret with IC<sub>50</sub> of 3 nM, 15 nM, and 48 nM, respectively. TG101348 has an IC<sub>50</sub> appr 300-fold higher for the closely related JAK3 and is a less potent inhibitor of the JAK1 and TYK2 family members. Fedratinib (TG-101348) inhibits proliferation of a human erythroblast leukemia (HEL) cell line that harbors the JAK2V617F mutation, as well as a murine pro-B cell line expressing human JAK2V617F (Ba/F3 JAK2V617F), with IC<sub>50</sub> of 305 nM and 270 nM, respectively. Fedratinib (TG-101348) also inhibits proliferation of parental Ba/F3 cells to a comparable level, with IC<sub>50</sub> of appr 420 nM. Fedratinib (TG-101348) treatment reduces STAT5 phosphorylation at concentrations that parallel the concentrations required to inhibit cell proliferation. Fedratinib (TG-101348) induces apoptosis in both HEL and Ba/F3 JAK2V617F cells in a dose-dependent manner. Fedratinib does not show proapoptotic activity in control normal human dermal fibroblasts at concentrations up to 10 μM, and the antiproliferative IC<sub>50</sub> against fibroblasts is &gt;5 μM[1]. Fedratinib (TG-101348) treatment decreases GATA-1 expression, which is associated with erythroid-skewing of JAK2V617F+ progenitor differentiation, and inhibits STAT5 as well as GATA S310 phosphorylation[2]. Fedratinib (TG-101348) inhibits the proliferation of HMC-1.1 (KITV560G) cells, with somewhat lower potency than HMC-1.2 (KITD816V, KITV560G) cells, with IC<sub>50</sub> of 740 nM and 407 nM, respectively[3].</p>			
<b>In Vivo</b>	<p>Fedratinib (TG-101348) has potential for efficacious treatment of JAK2V617F-associated myeloproliferative diseases (MPD). In treated animals, there is a statistically significant reduction in hematocrit and leukocyte count, a dose-dependent reduction/elimination of extramedullary hematopoiesis, and, at least in some instances, evidence for attenuation of myelofibrosis, correlated with surrogate endpoints, including reduction/elimination of JAK2V617F disease burden, suppression of endogenous erythroid colony formation, and in vivo inhibition of JAK-STAT signal transduction. There are no apparent toxicities and no effect on T cell number[1]. Oral administration of Fedratinib (TG-101348) (120 mg/kg) significantly inhibits PV progenitor erythroid differentiation in vivo[2].</p>			
	<p><b><i>In Vitro:</i></b></p> <p><b>DMSO : ≥ 42 mg/mL (80.05 mM)</b></p> <p><b>H<sub>2</sub>O : &lt; 0.1 mg/mL (insoluble)</b></p> <p>* "≥" means soluble, but saturation unknown.</p>			
	<b>Preparing Stock Solutions</b>	<b>Solvent</b>	<b>Mass</b>	
		<b>Concentration</b>		
		<b>1 mM</b>	<b>1.9059 mL</b>	<b>9.5296 mL</b>
		<b>5 mM</b>	<b>0.3812 mL</b>	<b>1.9059 mL</b>
		<b>10 mM</b>	<b>0.1906 mL</b>	<b>0.9530 mL</b>
	<p>*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> <p>储备液的保存方式和期限 -80℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用，-20℃</p>			

Solvent&Solubility	<p>储存时，请在 1 个月内使用。</p> <p><b><i>In Vivo:</i></b></p> <p>请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 <b>In Vitro</b> 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (4.76 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (4.76 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 400 <math>\mu</math>L PEG300 中，混合均匀；向上述体系中加入 50 <math>\mu</math>L Tween-80，混合均匀；然后继续加入 450 <math>\mu</math>L 生理盐水定容至 1 mL</p> <p>2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-<math>\beta</math>-CD in saline) Solubility: 2.5 mg/mL (4.76 mM); Suspended solution; Need ultrasonic</p> <p>此方案可获得 2.5 mg/mL (4.76 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 20% 的 SBE-<math>\beta</math>-CD 生理盐水水溶液中，混合均匀。</p> <p>3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.76 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (4.76 mM, 饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 玉米油中，混合均匀。</p>
References	<p>[1]. Wernig G, et al. Efficacy of TG101348, a selective JAK2 inhibitor, in treatment of a murine model of JAK2V617F-induced polycythemia vera. <i>Cancer Cell</i>. 2008 Apr;13(4):311-20.</p> <p>[2]. Geron I, et al. Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors. <i>Cancer Cell</i>. 2008 Apr;13(4):321-30.</p> <p>[3]. Lasho T, et al. Inhibition of JAK-STAT signaling by TG101348: a novel mechanism for inhibition of K1TD816V-dependent growth in mast cell leukemia cells. <i>Leukemia</i>. 2010 Jul;24(7):1378-80.</p> <p>[4]. Mu CF, et al. Codelivery of AP24534 and SAR302503 by Active Bone-Targeted Polymeric Micelles for the Treatment of Therapy-Resistant Chronic Myeloid Leukemia. <i>Mol Pharm</i>. 2017 Jan 3;14(1):274-283.</p>
实验参考：	
Cell Assay	<p>Approximately <math>2 \times 10^3</math> cells are plated into microtiter-plate wells in 100 <math>\mu</math>L RPMI-1640 growth media with indicated concentrations of inhibitor. Following 72 hours incubation with Fedratinib, 50 <math>\mu</math>L of XTT dye are added to each well and incubated for 4 hours in a CO<sub>2</sub> incubator. The colored formazan product is measured by spectrophotometry at 450 nm with correction at 650 nm. The concentration in which 50% of the effect (i.e., inhibition of proliferation) is observed (IC<sub>50</sub>) is determined using the GraphPad Prism 4.0 software. All experiments are performed in triplicate, and the results are normalized to growth of untreated cells. Induction of apoptosis of EpoBa/F3 JAK2V617F, Ba/F3p210, HEL, and K562 cells is determined by DNA fragmentation with DMSO and increasing concentrations of Fedratinib. [1]</p>

<b>Animal Administration</b>	<p>Briefly, C57BL/6 mice are intravenously injected with <math>1 \times 10^6</math> whole bone marrow expressing JAK2V617F. Full development of disease is assessed with differential peripheral blood counts at day 26 after bone marrow transplantation. Fedratinib (TG-101348) is administered by oral gavage twice daily (b.i.d.) at 60 mg/kg, 120 mg/kg, or placebo from day 28 on for 42 days. Differential blood counts are assessed by retro-orbital nonlethal eyebleeds using EDTA glass capillary tubes before study initiation, during the study, and at study endpoints. C57/BL6 mice are sacrificed at study endpoint or at times indicated based on an IUCAC-approved protocol that includes assessment of morbidity by &gt; 10% loss of weight, scruffy appearance, lethargy, and/or splenomegaly extending across the midline. For histopathology, tissues are fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin and eosinor, to assess for fibrosis, stained with reticulin. [1]</p>
<b>References</b>	<p>[1]. <a href="#">Wernig G, et al. Efficacy of TG101348, a selective JAK2 inhibitor, in treatment of a murine model of JAK2V617F-induced polycythemia vera. Cancer Cell. 2008 Apr;13(4):311-20.</a></p> <p>[2]. <a href="#">Geron I, et al. Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors. Cancer Cell. 2008 Apr;13(4):321-30.</a></p> <p>[3]. <a href="#">Lasho T, et al. Inhibition of JAK-STAT signaling by TG101348: a novel mechanism for inhibition of KITD816V-dependent growth in mast cell leukemia cells. Leukemia. 2010 Jul;24(7):1378-80.</a></p> <p>[4]. <a href="#">Mu CF, et al. Codelivery of AP24534 and SAR302503 by Active Bone-Targeted Polymeric Micelles for the Treatment of Therapy-Resistant Chronic Myeloid Leukemia. Mol Pharm. 2017 Jan 3;14(1):274-283.</a></p>

源叶生物