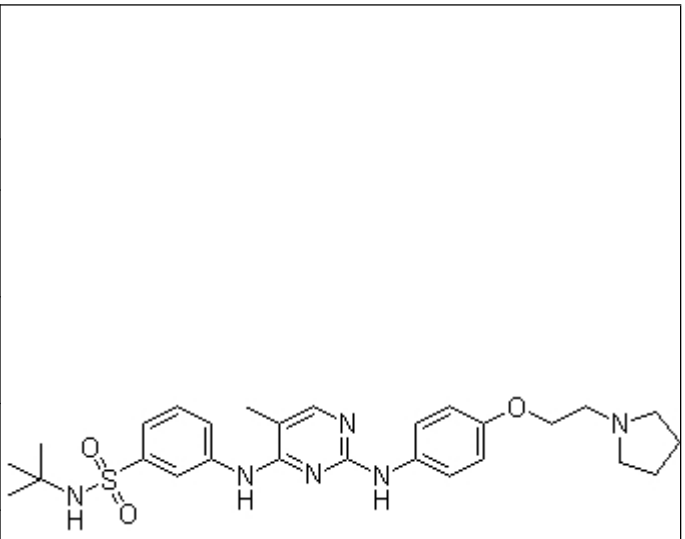
Product Introduction

TG101348 (SAR302503)

TG-101348 (SAR302503) is a selective inhibitor of **JAK2** with **IC50** of 3 nM, 35- and 334-fold more selective for JAK2 versus JAK1 and JAK3. Phase 1/2.

Technical Data:

Molecular Weight (MW):	524.68	
Formula:	$C_{27}H_{36}N_6O_3S$	
Solubility (25°C) *** <1 mg/ml means slightly soluble or insoluble:**	DMSO 100 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	936091-26-8	

Biological Activity

TG-101348 also significantly inhibits JAK2 V617F, Flt3, and Ret with IC50 of 3 nM, 15 nM, and 48 nM, respectively. TG101348 has an IC50 ~300-fold higher for the closely related JAK3 and is a less potent inhibitor of the JAK1 and TYK2 family members. TG101348 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 IC50 of 305 nM and 270 nM, respectively. TG-101348 also inhibits proliferation of parental Ba/F3 cells to a comparable level, with IC50 of ~420 nM.

TG101348 treatment reduces STAT5 phosphorylation at concentrations that parallel the concentrations required to inhibit cell proliferation. TG101348 induces apoptosis in both HEL and Ba/F3 JAK2V617F cells in a dose-dependent manner. TG101348 does not show proapoptotic activity in control normal human dermal fibroblasts at concentrations up to 10 μM, and the antiproliferative IC50 against fibroblasts is >5 μM. [1] TG101348 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] TG101348 inhibits the proliferation of HMC-1.1 (KITV560G) cells, with somewhat lower potency than HMC-1.2 (KITD816V, KITV560G) cells, with IC50 of 740 nM and 407 nM, respectively. [3]

TG101348 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 TG101348 (120 mg/kg) significantly inhibits PV progenitor erythroid differentiation in vivo. [2]

References

[1] Wernig G, et al. Cancer Cell, 2008, 13(4), 311-320.

[2] Geron I, et al. Cancer Cell, 2008, 13(4), 321-330.

[3] Lasho T, et al. Leukemia, 2010, 24(7), 1378-1380.

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