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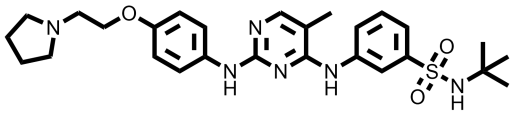
JAK2 and BRD4 Dual Inhibitor – TG101348 (SAR302503)

Chemical Name: N-(tert-butyl)-3-((5-methyl-2-((4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)pyrimidin-4-yl)amino)benzenesulfonamide



Molecular Weight:	524.68
Formula:	$C_{27}H_{36}N_6O_3S$
Purity:	≥98%
CAS#:	936091-26-8
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

TG101348 is a potent, specific and orally bioavailable inhibitor of JAK2 (IC_{50} ~3 nM) and BRD4 (IC_{50} ~164 nM). It is 35- and 334-fold more selective for JAK2 versus JAK1 and JAK3. It also significantly inhibits JAK2 V617F, Flt3, and Ret with IC50 of 3 nM, 15 nM, and 48 nM, respectively. TG101348 induces apoptosis in both HEL and Ba/F3 JAK2V617F cells, but not in normal human dermal fibroblasts at concentrations up to 10 uM, and its antiproliferative IC_{50} against fibroblasts is > 5 uM. In a UT7/EPO cell line, TG101348 inhibited STAT5 phosphorylation at 600 nM and inhibited AKT phosphorylation while reducing GATA-1 S310 phosphorylation. It also displaces BRD4 from chromatin and suppresses c-Myc expression. The combination of inhibitory activities on independent kinase and bromodomain oncogenic pathways exemplifies a new strategy for rational single-agent polypharmacological targeting.

How to Use:

In vitro: TG101348 was used at 1 μM in vitro.

In vivo: TG101348 was dosed to mice orally at 120 mg/kg twice per day in xenograft models.

Reference:

1. Wernig G, et al. Efficacy of TG101348, a selective JAK2 inhibitor, in treatment of a murine model of JAK2V617F-induced polycythemia vera. (2008) Cancer Cell. 13(4):311-20.
2. Geron I, et al. Selective inhibition of JAK2-driven erythroid differentiation of polycythemia vera progenitors. (2008) Cancer Cell. 13(4):321-30.
3. 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. (2010) Leukemia. 24(7):1378-80.
4. Ciceri P, et al. Dual kinase-bromodomain inhibitors for rationally designed polypharmacology. (2014) Nat Chem Biol. In press.