Product Data Sheet

Product Name: TG 100572
Cat. No.: GC37771

Chemical Properties

Cas. No.	867334-05-2		
SMILES	ClC1=CC=C(O)C=C1C2=CC(C)=C(N=C(NC(C=C3)=CC=C3OCCN4CCCC4)N=N5)C5=C2		
Formula	$C_{26}H_{26}ClN_5O_2$	M.Wt	475.97
Solubility	DMSO: ≥ 150 mg/mL (315.15 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	TG 100572		

Protocol

Cell experiment:

For proliferation assays, human retinal microvascular EC plated in 96-well cluster plates are cultured for 48 hr in the presence of either TG 100572 (2 nM-5 μM) or DMSO; medium contained 10% FBS, 50 μg/mL heparin, and 50 ng/mL rhVEGF. Cell numbers are then assessed using an XTT-based assay[1].

Animal experiment:

Mice: C57BL/6 mice (15-20 g) are dosed i.p. twice daily for 4 days with 5 mg/ kg TG 100572, followed by a single dose on Day 5, 5 hr after which plasma samples are taken, animals euthanized, and eyes explanted. Alternatively, mice are dosed topically with either TG 100572 or related prodrugs (e.g., TG 100801) by delivering a single 10 μL drop to both eyes for a total of two days, and both plasma and eyes harvested prior to or 0.5, 1, 3, 5, or 7 hr after the Day 2 dosing[1].

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References:

[1]. Doukas J, et al. Topical administration of a multi-targeted kinase inhibitor suppresses choroidal neovascularization and retinal edema. J Cell Physiol. 2008 Jul;216(1):29-37.
[2]. Palanki MS, et al. Development of prodrug 4-chloro-3-(5-methyl-3-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}-1,2,4-benzotriazin-7-yl)phenyl benzoate (TG100801): a topically administered therapeutic candidate in clinical trials for the treatment of age-related macular degeneration. J Med Chem. 2008 Mar 27;51(6):1546-59.

Background

TG 100572 is a multi-targeted kinase inhibitor which inhibits receptor tyrosine kinases and Src kinases; has IC50s of 2, 7, 2, 16, 13, 5, 0.5, 6, 0.1, 0.4, 1, 0.2 nM for VEGFR1, VEGFR2, FGFR1, FGFR2, PDGFRβ, Fgr, Fyn, Hck, Lck, Lyn, Src, Yes, respectively. VEGFR1|2 nM (IC50)|VEGFR2|7 nM (IC50)|FGFR1|2 nM (IC50)|FGFR2|16 nM (IC50)|PDGFRβ|13 nM (IC50)

TG 100572 shows sub-nanomolar activity against the Src family as well as RTK such as VEGFR1 and R2, FGFR1 and R2, and PDGFRβ. TG 100572 inhibits vascular endothelial cell proliferation (ED50=610±71 nM) and blocks VEGF-induced phosphorylation of extracellular signal-regulated kinase. TG 100572 induces apoptosis in rapidly proliferating, but not quiescent, endothelial cell cultures[1]. TG 100572 is shown to inhibit hRMVEC cell proliferation, with an IC50 of 610±72 nM. This suggests that TG 100572 has the therapeutic potential to inhibit VEGF function in ocular endothelial cells, a contributing factor to pathological angiogenesis in diseases such as AMD and PDR[2].

Systemic delivery of TG 100572 in a murine model of laser-induced choroidal neovascularization (CNV) causes significant suppression of CNV, but with an associated weight loss suggestive of systemic toxicity[1]. A concentration of 23.4 μM (Cmax) of TG 100572 is reached in 30 min (Tmax)=0.5 h) in the choroid and the sclera. However, the levels of TG 100572 in the retina are relatively low. The half-life of TG 100572 in ocular tissues is very short; hence, the compound is administered topically minimum t.i.d. to maintain appropriate drug levels in the eye. The

maximum concentration one can achieve in formulations using TG 100572 is 0.7% w/v[2].

[1]. Doukas J, et al. Topical administration of a multi-targeted kinase inhibitor suppresses choroidal neovascularization and retinal edema. J Cell Physiol. 2008 Jul;216(1):29-37. [2]. Palanki MS, et al. Development of prodrug 4-chloro-3-(5-methyl-3-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}-1,2,4-benzotriazin-7-yl)phenyl benzoate (TG100801): a topically administered therapeutic candidate in clinical trials for the treatment of age-related macular degeneration. J Med Chem. 2008 Mar 27;51(6):1546-59.

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