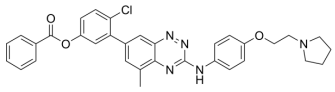
TG 100801

Cat. No.:	HY-10186
CAS No.:	867331-82-6
Molecular Formula:	$C_{33}H_{30}ClN_5O_3$
Molecular Weight:	580.08
Target:	VEGFR; FGFR; PDGFR; Src
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 5.56 mg/mL (9.58 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7239 mL	8.6195 mL	17.2390 mL
	5 mM	0.3448 mL	1.7239 mL	3.4478 mL
	10 mM	---	---	---

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

TG 100801 is a proagent that generates TG 100572 by de-esterification in development to treat age-related macular degeneration. TG 100572 is a multi-targeted kinase inhibitor which inhibits receptor tyrosine kinases and Src kinases; has IC_{50}s of 2, 7, 2, 16, 13, 5, 0.5, 6, 0.1, 0.4, 1, 0.2 for VEGFR1, VEGFR2, FGFR1, FGFR2, PDGFRβ, Fgr, Fyn, Hck, Lck, Lyn, Src, Yes, respectively.

IC_{50} & Target

VEGFR1 2 nM (IC_{50})	VEGFR2 7 nM (IC_{50})	FGFR1 2 nM (IC_{50})	FGFR2 16 nM (IC_{50})
PDGFRβ 13 nM (IC_{50})			

In Vitro

TG 100801 is a topically administered prodrug delivered as an eye drop that is readily converted to the active TG 100572 in the eye.TG 100572 is shown to inhibit hRMVEC cell proliferation, with an IC_{50} of 610±72 nM[1]. TG 100801 is formed by derivitization of a phenolic moiety in TG100572 to yield an ester. It displays excellent balance of stability (physical and chemical) with hydrolysis rate. On its own, TG 100801 does not display meaningful anti-kinase activity, as the ester group

	blocks key interactions with kinase active sites, however exposure to esterases (abundant in mammalian tissues) rapidly liberates active TG100572.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 (ED_{50}=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[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	TG 100801 exhibits excellent ocular pharmacokinetics and poor systemic circulation and shows good efficacy in the laser induced choroidal neovascularization model. A concentration of 23.4 μM (C_{max}) of TG 100572 is reached in 30 min (T_{max})=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[1]. TG 100801 nor TG100572 are detectable in plasma following topical delivery of TG 100801, and adverse safety signals (such as weight loss) are not observed even with prolonged dosing schedules. Topical TG 100801 significantly suppresses laser-induced choroidal neovascularlization in mice, and reduces fluorescein leakage from the vasculature and retinal thickening measured by optical coherence tomography in a rat model or retinal vein occlusion.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[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2]	Rats: Long Evans rats are dosed topically in both eyes with 10 μL of TG 100801 (as a 0.3, 0.6 or 1% solution) or vehicle. A total of 5 topical applications are delivered per eye over a three day period: dosing is performed one hour prior to and six hours after laser-induced thrombosis on Day 1, twice on Day 2, and once the morning of Day 3. One hour after the final topical application, retinal edema is assessed by one of two means[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.

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REFERENCES

[1]. 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.

[2]. Doukas, John, et al. Topical administration of a multi-targeted kinase inhibitor suppresses choroidal neovascularization and retinal edema. Journal of Cellular Physiology (2008), 216(1), 29-37.

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