Toceranib phosphate

Cat. No.: HY-10330A

CAS No.: 874819-74-6

Molecular Formula: $C_{22}H_{28}FN_4O_6P$

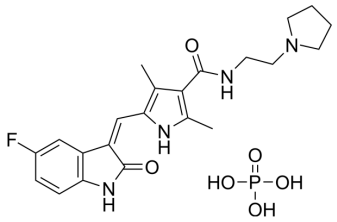
Molecular Weight: 494.45

Target: PDGFR; VEGFR; c-Kit

Pathway: Protein Tyrosine Kinase/RTK

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 2.46 mg/mL (4.98 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0224 mL	10.1122 mL	20.2245 mL
	5 mM	---	---	---
	10 mM	---	---	---

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

BIOLOGICAL ACTIVITY

Description

Toceranib phosphate (SU11654 phosphate) is an orally active receptor tyrosine kinase (RTK) inhibitor, and it potently inhibits PDGFR, VEGFR, and Kit with K_is of 5 and 6 nM for PDGFRβ and Flk-1/KDR, respectively. Toceranib phosphate (SU11654 phosphate) has antitumor and antiangiogenic activity, and used in the treatment of canine mast cell tumors[1] [2].

IC_{50} & Target

PDGFRβ	Flk-1
5 nM (Ki)	6 nM (Ki)

In Vitro

Toceranib phosphate (PHA 291639 phosphate) is a selective inhibitor of the tyrosine kinase activity of several members of the split kinase RTK family, including PDGFR and Flk-1/KDR, with K_is of 5 and 6 nM, respectively[1].

To explore mechanisms of acquired Toceranib (TOC) resistance in canine MCT, three resistant sublines are generated from the Toceranib-sensitive exon 11 ITD c-kit mutant C2 cell line designated TR1, TR2, and TR3. Growth of the parental C2 cells is inhibited by Toceranib in a dose-dependent manner with an IC_{50} of <10 nM. In contrast, TR1, TR2, and TR3 sublines are resistant to inhibition by Toceranib (IC_{50}> 1,000 nM). Sensitivity to three other KIT RTK inhibitors is similar to the observed resistance to Toceranib. The parental line as well as all three sublines retains sensitivity to the cytotoxic agents vinblastine (VBL) and CCNU. Following 72 hr culture in the presence of increasing concentrations of Toceranib, treatment naïve, parental C2 cells detach from the culture flask and become rounded, shrunken, and clumped with increased exposure to Toceranib. In contrast, Toceranib-induced morphologic differences are not identified in the resistant sublines[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Administration of Toceranib phosphate (PHA 291639 phosphate) significantly decreases the number and percentage of Treg in the peripheral blood of dogs with cancer. Dogs receiving Toceranib phosphate (PHA 291639 phosphate) and cyclophosphamide (CYC) demonstrate a significant increase in serum concentrations of IFN-γ, which is inversely correlated with Treg numbers after 6 weeks of combination treatment[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	The ***c-kit*** mutant canine C2 mastocytoma cell line, derived from a spontaneously occurring cutaneous mast cell tumors (MCTs), is used as the parental cell line. Cells are propagated in RPMI 1640 supplemented with 2 mM L-glutamine, 10% FBS, 100 g/mL Streptomycin, and 100 U/mL Penicillin in a 37°C incubator under a humidified atmosphere of 5% CO_2. Toceranib-resistant C2 cells are selected by growing C2 cells in concentrations of Toceranib ranging from 0.02 uM to 0.3 uM and increasing in 0.025-0.05 uM increments. Three independent, Toceranib -resistant sublines are established over a period of 7 months[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Dogs[3] Fifteen client-owned dogs with advanced tumors are used. Dogs receive Toceranib at 2.75 mg/kg once every other day. After 2 weeks, oral cyclophosphamide (CYC) is added at 15 mg/m^2 daily. Numbers of Treg and lymphocyte subsets are measured in blood by flow cytometry during the 8-week study period. Serum concentrations of IFN-γ are measured by ELISA. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. London CA, et al. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies. Clin Cancer Res. 2003 Jul;9(7):2755-68.

[2]. Halsey CH, et al. Development of an in vitro model of acquired resistance to toceranib phosphate (Palladia?) in canine mast cell tumor. BMC Vet Res. 2014 May 6;10:105.

[3]. Mitchell L, et al. Clinical and immunomodulatory effects of toceranib combined with low-dose cyclophosphamide in dogs with cancer. J Vet Intern Med. 2012 Mar-Apr;26(2):355-62.

[4]. London C, Mathie T, Stingle N, et al. Preliminary evidence for biologic activity of toceranib phosphate (Palladia(®)) in solid tumours. Vet Comp Oncol. 2012;10(3):194-205.

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