Tarloxotinib bromide

Cat. No.: HY-17632

CAS No.: 1636180-98-7

Molecular Formula: $C_{24}H_{24}Br_2ClN_9O_3$

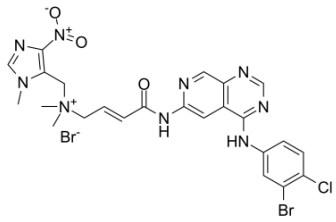
Molecular Weight: 681.77

Target: EGFR

Pathway: JAK/STAT Signaling; Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 33 mg/mL (48.40 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.4668 mL	7.3339 mL	14.6677 mL
5 mM	0.2934 mL	1.4668 mL	2.9335 mL
10 mM	0.1467 mL	0.7334 mL	1.4668 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (3.67 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (3.67 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tarloxotinib bromide (TH-4000) is an irreversible EGFR/HER2 inhibitor.

IC_{50} & Target

EGFR/HER2

In Vitro

To confirm the mechanism of action, Tarloxotinib bromide is shown to be metabolized efficiently under hypoxia using a panel of human NSCLC cell lines (rate of TKI release 0.4-2.1 nM/hr/10^6 cells), a process that is inhibited by oxygen (TKI release <0.002 nM/hr/10^6 cells). Cellular anti-proliferative and receptor phosphorylation assays demonstrate a 14-80 fold reduction of Tarloxotinib bromide activity relative to TKI. Using PC9 tumors, hyperbaric oxygen breathing suppresse release of TKI from Tarloxotinib bromide by >80% (538 vs 99 nM/kg; p<0.01) compared to air breathing controls. Collectively, these

	data further validate that Tarloxotinib bromide is a hypoxia-activated irreversible EGFR-TKI, and show that Tarloxotinib bromide has greater activity compared with erlotinib[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	A prototypic WT EGFR driven xenograft model (A431) is used to benchmark Tarloxotinib bromide activity against each EGFR-TKI by “retrotranslation” of reported plasma exposure for each agent in human subjects back to the xenograft model. Only treatment with clinically relevant doses and schedules of Tarloxotinib bromide is associated with tumor regression and durable inhibition of WT EGFR tumor phosphorylation. Consistent with these findings, Tarloxotinib bromide treatment can also regress the WT EGFR NSCLC tumor models H125 and H1648, demonstrating Tarloxotinib bromide provides the necessary therapeutic index to inhibit WT EGFR in vivo[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Shevan Silva, Abstract A67: Preclinical efficacy of tarloxotinib bromide (TH-4000), a hypoxia-activated EGFR/HER2 inhibitor: rationale for clinical evaluation in EGFR mutant, T790M-negative NSCLC following progression on EGFR-TKI therapy. Abstracts: AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; November 5-9, 2015; Boston, MA.

[2]. Adam V. Patterson, Abstract 5358: The hypoxia-activated EGFR-TKI TH-4000 overcomes erlotinib-resistance in preclinical NSCLC models at plasma levels achieved in a Phase 1 clinical trial. AACR 106th Annual Meeting 2015; April 18-22, 2015; Philadelphia, PA.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA