Tarloxotinib bromide

Cat. No.: HY-17632
CAS No.: 1636180-98-7
Molecular Formula: C₂₄H₂₄Br₂ClN₉O₃
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.

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>1.4668 mL</td>
<td>7.3339 mL</td>
<td>14.6677 mL</td>
<td></td>
</tr>
<tr>
<td>5 mM</td>
<td>0.2934 mL</td>
<td>1.4668 mL</td>
<td>2.9335 mL</td>
<td></td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1467 mL</td>
<td>0.7334 mL</td>
<td>1.4668 mL</td>
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</tr>
</tbody>
</table>

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 2.5 mg/mL (3.67 mM); Clear solution

BIOLOGICAL ACTIVITY

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

IC₅₀ & 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/10⁶ cells), a process that is inhibited by oxygen (TKI release <0.002 nM/hr/10⁶ 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 suppresses 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\[^2\].

<table>
<thead>
<tr>
<th>In Vivo</th>
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<tbody>
<tr>
<td>A prototypic WT EGFR driven xenograft model (A431) is used to benchmark Tarloxotinib bromide activity against each EGFR-TKI by “retroattribution” 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].</td>
</tr>
</tbody>
</table>

**REFERENCES**

\[^1\]. Shevan Silva, Abstract A67: Preclinical efficacy of tarloxotin 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.