Tirabrutinib

Cat. No.: HY-15771

CAS No.: 1351636-18-4

Molecular Formula: $C_{25}H_{22}N_6O_3$

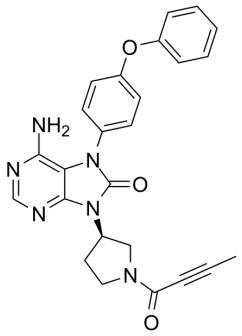
Molecular Weight: 454.48

Target: Btk; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Apoptosis

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 : ≥ 100 mg/mL (220.03 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2003 mL	11.0016 mL	22.0032 mL
5 mM	0.4401 mL	2.2003 mL	4.4006 mL
10 mM	0.2200 mL	1.1002 mL	2.2003 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 (5.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.50 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tirabrutinib (ONO-4059) is an orally active Bruton's Tyrosine Kinase (BTK) inhibitor (can cross the blood-brain barrier (BBB)), with an IC_{50} of 6.8 nM. Tirabrutinib irreversibly and covalently binds to BTK and inhibits aberrant B cell receptor signaling. Tirabrutinib can be used in studies of autoimmune diseases and hematological malignancies[1][2][3][4].

In Vitro

Tirabrutinib (0.1-1000 nM or 0.001-100 nM; 72 h) inhibits the proliferation of OCI-L Y10 and SU-DHL-6 cells with IC_{50}s of 9.127 nM, and 17.10 nM, respectively[1].

Tirabrutinib (0.5, 5, 50 μM; 24, 48 h) induces SU-DHL-6 cells apoptosis needs high dosage and prolonged administration (concentration up to 50 μM and incubates for 48 h)[1].
Tirabrutinib (300 nM, 72 h) induces caspase-3 and PARP cleavage in TMD8 cells[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[1]

Cell Line:	SU-DHL-6 and OCI-L Y10 cells
Concentration:	0.1-1000 nM; 0.001 nM-100 nM
Incubation Time:	72 h
Result:	Showed good anti-proliferative activity with IC_{50}s of 9.127 nM, and 17.10 nM for OCI-L Y10 and SU-DHL-6 cells, respectively.

Apoptosis Analysis[1]

Cell Line:	SU-DHL-6 cells
Concentration:	0.5, 5, 50 μM
Incubation Time:	24, 48 h
Result:	Induced cell apoptosis when concentration up to 50 μM and incubated for 48 h.

Western Blot Analysis[2]

Cell Line:	TMD8 cells
Concentration:	300 nM
Incubation Time:	72 h
Result:	Induced caspase-3 and PARP cleavage.

In Vivo

Tirabrutinib (10 mg/kg; p.o.; single) is rapidly absorbed into plasma and brain, and reaches C_{max} (blood C_{max} =339.53 ng/mL; brain C_{max} =28.9 ng/mL) 2 hours post administration[1].
Tirabrutinib (6, 20 mg/kg; p.o.; single daily for 3 weeks) shows inhibition of tumour growth in vivo[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male SD rats (219.0–260.5g)[1].
Dosage:	10 mg/kg
Administration:	Oral administration; single.
Result:	Pharmacokinetic Parameters of Tirabrutinib in male SD rats[1].

	Plasma, C_{max} (ng/mL)	Brain, C_{max} (ng/mL)	Penetration rate (%, $C_{max, brain}/C_{max, plasma}$)
PO (10 mg/kg)	339.53	28.9	8.5

Animal Model:	Immunodeficiency (SCID) mice (mouse xenograft model)[2].
Dosage:	6, 20 mg/kg
Administration:	Oral administration; single daily for 3 weeks.
Result:	Inhibited tumour growth, and when dosage up to 20 mg/kg, a complete tumor suppression at day 14.

CUSTOMER VALIDATION

- Stem Cell Reports. 2019 May 14;12(5):996-1006.
- Rapid Commun Mass Spectrom. 2021 Dec 14;e9240.

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REFERENCES

[1]. Yu H, et al. Bruton's tyrosine kinase inhibitors in primary central nervous system lymphoma-evaluation of anti-tumor efficacy and brain distribution. Transl Cancer Res. 2021 May;10(5):1975-1983.

[2]. Kozaki R, et al. Responses to the Selective Bruton's Tyrosine Kinase (BTK) Inhibitor Tirabrutinib (ONO/GS-4059) in Diffuse Large B-cell Lymphoma Cell Lines. Cancers (Basel). 2018 Apr 23;10(4):127.

[3]. Liclican A, et al. Biochemical characterization of tirabrutinib and other irreversible inhibitors of Bruton's tyrosine kinase reveals differences in on - and off - target inhibition. Biochim Biophys Acta Gen Subj. 2020 Apr;1864(4):129531.

[4]. Dhillon S. Tirabrutinib: First Approval. Drugs. 2020 Jun;80(8):835-840.

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