Tamnorzatinib

Cat. No.: HY-114358

CAS No.: 1646839-59-9

Molecular Formula: $C_{32}H_{26}N_4O_6$

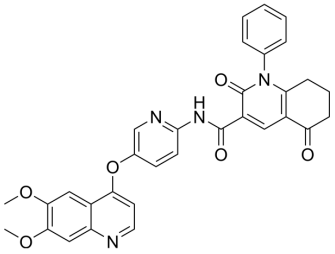
Molecular Weight: 562.57

Target: TAM Receptor; Trk Receptor

Pathway: Protein Tyrosine Kinase/RTK; Neuronal Signaling

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 : 250 mg/mL (444.39 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7776 mL	8.8878 mL	17.7756 mL
	5 mM	0.3555 mL	1.7776 mL	3.5551 mL
	10 mM	0.1778 mL	0.8888 mL	1.7776 mL

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

BIOLOGICAL ACTIVITY

Description

Tamnorzatinib (ONO-7475) is a potent, selective, and orally active Axl/Mer inhibitor with IC50 values of 0.7 nM and 1.0 nM, respectively. Tamnorzatinib sensitizes AXL-overexpressing EGFR-mutant NSCLC cells to the EGFR-TKIs, suppresses the emergence and maintenance of tolerant cells. Tamnorzatinib combines with Osimertinib (HY-15772) provides a bright promise for the study of EGFR-mutated non-small cell lung cancer (NSCLC).

IC_{50} & Target

TrkA

In Vitro

Tamnorzatinib is against recombinant human AXL with IC_{50} values of 0.414 nM and 0.7 nM in off-chip MSA and ACD cell-based tyrosine kinase assay, respectively. It is against AXL, MER, TYRO3, TRKB, PDGFR alpha, TRKA, and FLT3 activities with IC_{50} values of 0.7 nM, 1.0 nM, 8.7 nM, 15.8 nM, 28.9 nM, 35.7 nM and 147 nM, respectively in a Cell-based Tyrosine Kinase assay[2].

Tamnorzatinib (0.0001 μM-1 μM; 72 hours) increases the sensitivity to Osimertinib and Dacomitinib and reduces the viability of high AXL-expressing PC-9 and HCC4011 cells, but not of low-AXL-expressing HCC827 cells. Besides, Tamnorzatinib enhances Osimertinib efficacy on the viability of cell lines PC-9, PC-9KGR, and HCC4011, and H1975, all of which express high levels of AXL. But it has a marginal effect on the viability of cell lines HCC827, HCC4006, and H3255 with low levels of AXL[1].

Tamnorzatinib (1 μM; 4 or 48 hours) combines with Osimertinib markedly inhibits the phosphorylation of AXL, AKT, and p70S6K compared with the treatment of the high-AXL-expressing cell lines treated with Osimertinib alone at 4 hours. It combines with osimertinib increases cleaved PARP in PC-9 and HCC4011 cells compared with the treatment with Osimertinib alone[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	High AXL-expressing cell: PC-9,HCC4011,H1975, PC-9KGR cells Low AXL-expressing cell: HCC827, HCC4006, and H3255 cells
Concentration:	0.0001 μM; 0.001 μM; 0.01 μM; 0.1 μM; 1 μM
Incubation Time:	72 hours
Result:	Increased the sensitivity and efficacy to Osimertinib in AXL-high level cells.

Western Blot Analysis[1]

Cell Line:	PC-9, HCC4011 cells
Concentration:	1 μM
Incubation Time:	4 or 48 hours
Result:	Increased p-AXL, AKT, and p70S6K expression at 4 hours and increases p-PARP expression at 48 hours when combindes with Osimertinib.

In Vivo

Tamnorzatinib (oral gavage; 10 mg/kg or combines with 5 mg/kg Osimertinib; 29 days) treatment alone has little effect on the tumor growth. Besides, Osimertinib alone causes tumor regression within one week, but the tumors reappear within three weeks. The combined initial treatment causes tumor regression and the size of tumors is maintained for 4 weeks. No apparent adverse events, including weight loss are observed during these treatments[1].

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Animal Model:	Mouse CDX model using high-AXL-expressing PC-9KGR cells (exon 19 deletion and the exon21-T790M mutation in EGFR)[1]
Dosage:	10 mg/kg; once daily; 19 days
Administration:	oral gavage
Result:	Had little effects alone, but combined treatments significantly decreased tumor volume without reappear.

REFERENCES

[1]. Okura N, et al. ONO-7475, a Novel AXL Inhibitor, Suppresses the Adaptive Resistance to Initial EGFR-TKI Treatment in EGFR-Mutated Non-Small Lung Cancer.Clin Cancer Res. 2020 Jan 17.

[2]. Ruvolo PP, et al. Anexelekto/MER tyrosine kinase inhibitor ONO-7475 arrests growth and kills FMS-like tyrosine kinase 3-internal tandem duplication mutant acute myeloid leukemia cells by diverse mechanisms.Haematologica. 2017 Dec;102(12):2048-2057.

Caution: Product has not been fully validated for medical applications. For research use only.

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