Osimertinib mesylate

Cat. No.: HY-15772A

CAS No.: 1421373-66-1

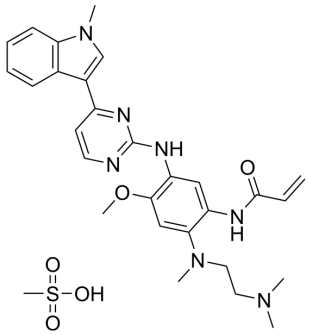
Molecular Formula: $C_{29}H_{37}N_7O_5S$

Molecular Weight: 595.71

Target: EGFR

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

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 2 years; -20°C, 1 year (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 13.89 mg/mL (23.32 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6787 mL	8.3933 mL	16.7867 mL
	5 mM	0.3357 mL	1.6787 mL	3.3573 mL
	10 mM	0.1679 mL	0.8393 mL	1.6787 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: ≥ 1.39 mg/mL (2.33 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.39 mg/mL (2.33 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.39 mg/mL (2.33 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Osimertinib mesylate (AZD9291 mesylate) is a covalent, orally active, irreversible, and mutant-selective EGFR inhibitor with an apparent IC_{50} of 12 nM against L858R and 1 nM against L858R/T790M. Osimertinib overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer[1].

IC_{50} & Target

$EGFR^{L858R/T790M}$	$EGFR^{L858R}$
1 nM (IC_{50})	12 nM (IC_{50})

In Vitro

Osimertinib (AZD-9291) shows similar potency to early generation tyrosine kinase inhibitor (TKIs) in inhibiting EGFR phosphorylation in EGFR cells harboring sensitising EGFR mutants including PC-9 (ex19del), H3255 (L858R) and H1650

(ex19del), with mean IC_{50} values ranging from 13 to 54 nM for Osimertinib. Osimertinib (AZD-9291) also potently inhibits phosphorylation of EGFR in T790M mutant cell lines (H1975 (L858R/T790M), PC-9VanR (ex19del/T790M), with mean IC_{50} potency less than 15 nM[1].

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

Cell Proliferation Assay[2]

Cell Line:	PC-9, H3255, PC-9ER, and H1975 cells
Concentration:	0.0001, 0.001, 0.01, 0.1, 1, 10 μM
Incubation Time:	72 hours
Result:	Dramatically inhibited cell proliferation (IC_{50}=41,26, 41, 31 nM, respectively)

Cell Proliferation Assay[2]

Cell Line:	Ba/F3 cells (harboring a T790M mutation, exon 19del+T790M, or L858R+T790M)
Concentration:	0.0001, 0.001, 0.01, 0.1, 1, 10 μM
Incubation Time:	72 hours
Result:	Inhibited cell proliferation (IC_{50} = 6, 7, 74 nM, respectively)

Cell Proliferation Assay[2]

Cell Line:	Ba/F3 cells (harboring EGFR exon 20 insertion mutations)
Concentration:	0.0001, 0.001, 0.01, 0.1, 1, 10 μM
Incubation Time:	72 hours
Result:	Inhibited cell proliferation (IC_{50} = 16, 701, 230, 38 nM, respectively)

Apoptosis Analysis[2]

Cell Line:	Ba/F3 cells(harboring EGFR exon 19del+T790M or EGFR L858R+T790M) [2]
Concentration:	0.1 μM
Incubation Time:	48 hours
Result:	Inducted apoptosis with the rate of 40.9% and 90% in EGFR T790M positive mutations cells respectively.

In Vivo

The tumor-bearing mice are treated with Osimertinib (AZD-9291) (5 mg/kg/day) for one to two weeks. Within days of treatment, 5 of 5 C/L858R mice displays nearly 80% reduction in tumor volume by magnetic resonance imaging MRI after therapy with Osimertinib, while 5 of 5 mice treated with vehicle shows tumor growth[1]. Osimertinib (AZD-9291) demonstrates improved rat PK, reduced hERG affinity, and improved IGF1R margins relative to the previously described compounds, and so this compound is selected for further investigation. Osimertinib (AZD-9291) also offers an additional degree of broader chemical and profile diversity when compared to the previously described lead compounds. Upon dosing Osimertinib (AZD-9291) in three efficacy models, The comparable efficacy is observed at relatively low doses (10 mg/kg per day). The excellent efficacy is also observed when Osimertinib (AZD-9291) is dosed at 5 mg/kg per day[2].

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Animal Model:	PC-9 (ex19del) and H1975 (L858R/T790M) tumor xenograft models[1]

Dosage:	0.1-10 mg/kg (PC-9 xenograft models); 0.5- 25 mg/kg (H1975 xenograft models)
Administration:	p.o.; daily for 14 day
Result:	Induced significant dose-dependent regression in both PC-9 (ex19del) and H1975 (L858R/T790M) tumor xenograft models.

CUSTOMER VALIDATION

- Cancer Cell. 2020 Jan 13;37(1):104-122.e12.
- Cancer Discov. 2019 Jul;9(7):926-943.
- Nat Cancer. 2023 Jun;4(6):829-843.
- Nat Cancer. 2022 Apr;3(4):402-417.
- ACS Nano. 2022 Jul 21.

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REFERENCES

[1]. Cross DA, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014 Sep;4(9):1046-61.

[2]. [2]Hirano T, et al. Pharmacological and Structural Characterizations of Naquotinib, a Novel Third-Generation EGFR Tyrosine Kinase Inhibitor, in EGFR-Mutated Non-Small Cell Lung Cancer. Mol Cancer Ther. 2018 Apr;17(4):740-750.

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