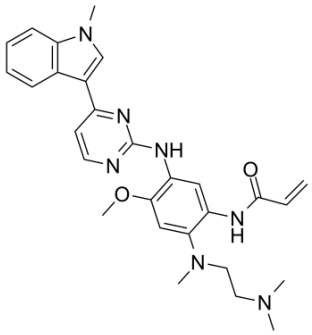
Osimertinib



Cat. No.: HY-15772

CAS No.: 1421373-65-0

Molecular Formula: $C_{28}H_{33}N_7O_2$

Molecular Weight: 499.61

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 : 100 mg/mL (200.16 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0016 mL	10.0078 mL	20.0156 mL
5 mM	0.4003 mL	2.0016 mL	4.0031 mL
10 mM	0.2002 mL	1.0008 mL	2.0016 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 (5.00 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.00 mM); Clear solution
3. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (5.00 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Osimertinib (AZD-9291) is an irreversible and mutant selective EGFR inhibitor with IC_{50}s of 12 and 1 nM against $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$, respectively[1].

IC_{50} & Target

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

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 AZD-9291. 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.
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 (AZD-9291), 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	PC-9 cells are seeded into T75 flasks (5×10^5 cells/flask) in RPMI growth media and incubated at 37°C, 5% CO_2. The following day the media is replaced with media supplemented with a concentration of EGFR inhibitor equal to the EC_{50} concentration predetermined in PC-9 cells. Media changes are carried out every 2-3 days and resistant clones allowed to grow to 80% confluency prior to the cells being trypsinised and reseeded at the original seeding density in media containing twice the concentration of EGFR inhibitor. Dose escalations are continued until a final concentration of 1.5 μM ZD1839, 1.5 μM BIBW 2992, 1.5 μM WZ4002 or 160 nM Osimertinib (AZD-9291) are achieved[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	Mice[1] The $EGFR^{L858R}$ and $EGFR^{L858R+T790M}$ mice (male and female) are used. Osimertinib (AZD-9291) is suspended in 1% Polysorbate 80 and administered via oral gavage once daily at the doses of 7.5 mg/kg and 5 mg/kg, respectively. Mice are imaged weekly at the Vanderbilt University Institute of Imaging Science. For immunoblot analysis, mice are treated for eight hours with drug as described before dissection and flash freezing of the lungs. Lungs are pulverized in liquid nitrogen before lysis. Rats[2] The male RccHan:WIST rats (10-week-old) are received a single oral dose of Osimertinib (AZD-9291) (200 mg/kg). Blood glucose levels are measured using an Accuchek Active meter. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Discov. 2019 Jul;9(7):926-943.
- Cancer Cell. 2020 Jan 13;37(1):104-122.e12.
- Theranostics. 2021 Jan 19;11(7):3392-3416.
- Cell Chem Biol. 2018 Aug 16;25(8):996-1005.e4.
- J Exp Clin Cancer Res. 2019 May 23;38(1):219.

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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]. Finlay MR, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistancemutations that spares the wild type form of the receptor. J Med Chem. 2014 Oct 23;57(20):8249-67.

India Contact:
Life Technologies (India) Pvt. Ltd.
306, Aggarwal City Mall, Opposite M2K Pitampura, Delhi – 110034 (INDIA). Ph: +91-11-42208000, 42208111, 42208222, Mobile: +91-9810521400, Fax: +91-11-42208444
Email: customerservice@lifetechindia.com Website: www.lifetechindia.com