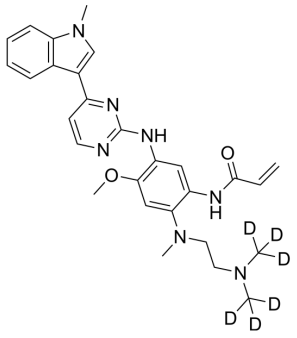
Osimertinib-d_6

Cat. No.:	HY-15772S
CAS No.:	1638281-44-3
Molecular Formula:	$C_{28}H_{27}D_6N_7O_2$
Molecular Weight:	505.64
Target:	EGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Storage:	4°C, protect from light, stored under nitrogen * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (197.77 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9777 mL	9.8885 mL	19.7769 mL
	5 mM	0.3955 mL	1.9777 mL	3.9554 mL
	10 mM	0.1978 mL	0.9888 mL	1.9777 mL

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

BIOLOGICAL ACTIVITY

Description

Osimertinib-d_6 is a deuterium labeled osimertinib. Osimertinib is a covalent, orally active, irreversible, and mutant-selective EGFR inhibitor with an apparent IC50 of 12 nM against L858R and 1 nM against L858R/T790M. Osimertinib overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer[1].

In Vitro

Osimertinib (AZD9291) (0-10 μM; 72 hours) dramatically inhibits cell proliferation with IC_{50}s of 41, 26, 41, and 31 nM, respectively[2].

Osimertinib (0-10 μM; 72 hours) inhibits cell proliferation (Ba/F3 cells harboring a T790M mutation, exon 19del+T790M, or L858R+T790M) with IC_{50}s of 6, 7, and 74 nM, respectively[2].

Osimertinib (0-10 μM; 72 hours) inhibits Ba/F3 cells harboring EGFR exon 20 insertion mutations (IC_{50} ranging from 16-701 nM for A763_Y764insFQEA (FQEA), Y764_V765insHH (HH), A767_V769dupASV (ASV), and D770_N771insNPG (NPG) cells) [2].

Osimertinib shows high levels of phenotype potency in both sensitizing-mutant (mean IC_{50} of 8 nM in PC-9) and T790M (mean IC_{50} of 11 and 40 nM in H1975 and PC-9VanR respectively) EGFR cell lines. Osimertinib has much less activity towards wild-type EGFR (mean IC_{50} of 650 and 461 nM in Calu3 and H2073 respectively)[1].

Osimertinib (0.1 μM; 48 hours) induces apoptosis in Ba/F3 cells (apoptosis rate of 40.9% and 90% in EGFR exon 19del+T790M, EGFR L858R+T790M respectively) [2].

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)

Apoptosis Analysis[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)
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

Osimertinib (0.1-25 mg/kg; p.o.; daily for 14 day) induces significant dose-dependent regression in both PC-9 (ex19del) and H1975 (L858R/T790M) tumor xenograft models[1].

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

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.

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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