Zipalertinib

Cat. No.: HY-112299

CAS No.: 1661854-97-2

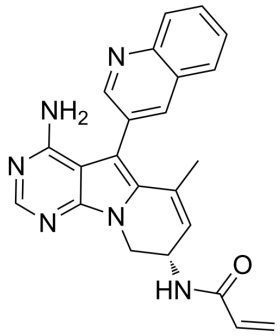
Molecular Formula: $C_{23}H_{20}N_6O$

Molecular Weight: 396.44

Target: EGFR; Apoptosis

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

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 : 22.73 mg/mL (57.34 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5224 mL	12.6122 mL	25.2245 mL
	5 mM	0.5045 mL	2.5224 mL	5.0449 mL
	10 mM	0.2522 mL	1.2612 mL	2.5224 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: ≥ 2.08 mg/mL (5.25 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.25 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.25 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Zipalertinib (TAS6417; CLN-081) is a highly effective, orally active and pan-mutation-selective EGFR tyrosine kinase inhibitor with a unique scaffold fitting into the ATP-binding site of the EGFR hinge region, with IC_{50} values ranging from 1.1-8.0 nM[1][2].

IC_{50} & Target

EGFR
1.1-8.0 nM (IC_{50})

In Vitro

Zipalertinib (TAS6417) inhibits EGFR phosphorylation and downstream molecules in NSCLC cell lines expressing EGFR exon

20 insertions, resulting in caspase activation[1].
Zipalertinib (TAS6417) is a robust inhibitor against the most common EGFR mutations (exon 19 deletions and L858R) and the most potent against cells harboring EGFR-T790M (1st/2nd generation TKI resistance mutation)[2].
Zipalertinib (TAS6417) covalently modified the cysteine residue at position 797 of recombinant EGFR harboring an in-frame insertion mutation in the exon 20 region[1].
Zipalertinib (TAS6417) inhibits EGFR signal transduction, leading to cell growth inhibition and apoptosis induction in NSCLC cells driven by EGFR exon 20 insertion mutations[1].
Zipalertinib (TAS6417) (0-10 μM) inhibits cell proliferation and EGFR signaling in NSCLC cell lines harboring EGFR common mutations in the presence or absence of T790M[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Apoptosis Analysis[2]

Cell Line:	PC-9, H1975, BID007, BID019, BEAS-2B cells.
Concentration:	0-10 μM.
Incubation Time:	24-48 h.
Result:	Led to apoptosis via inhibition of mutant EGFR.

In Vivo

Zipalertinib (TAS6417) (10-200 mg/kg) causes persistent tumor regression in vivo in EGFR exon 20 insertion-driven tumor models. TAS6417 inhibits mutant EGFR in tumors but not WT EGFR in skin tissues[1].
Zipalertinib (TAS6417) had no effect on EGFR-independent proliferation in NCI-H23 or NCI-H460 cells[1].
Zipalertinib (TAS6417) administered at 20 mg/kg, which achieves complete suppression of tumor growth, induces a significant decrease in pEGFR, leading to reduction of pAKT and pERK at 1 h. The inhibitory effect is still noted at 6 h, and phosphorylation of EGFR, ATK, and ERK recovered by 24 h[1].
Zipalertinib (TAS6417) (100 and 200 mg/kg/day) prolongs survival of animals bearing lung cancer[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Mice implanted with NCI-H1975 EGFR D770_N771insSVD xenografts[1].
Dosage:	50 and 100 mg/kg.
Administration:	Orally once daily for 14 days.
Result:	Showed marked tumor growth inhibition with treatment/control (T/C) ratios of 51% and 19%, respectively.

REFERENCES

[1]. Hasako S, et al. TAS6417, A Novel EGFR Inhibitor Targeting Exon 20 Insertion Mutations. Mol Cancer Ther. 2018 Aug;17(8):1648-1658.

[2]. Hibiki Udagawa, et al. TAS6417/CLN-081 Is a Pan-Mutation-Selective EGFR Tyrosine Kinase Inhibitor with a Broad Spectrum of Preclinical Activity against Clinically Relevant EGFR Mutations. Mol Cancer Res. 2019 Nov;17(11):2233-2243.

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