EAI045

Cat. No.: HY-100213

CAS No.: 1942114-09-1

Molecular Formula: $C_{19}H_{14}FN_3O_3S$

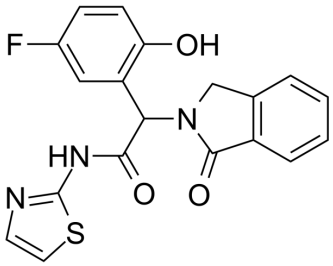
Molecular Weight: 383.4

Target: EGFR

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

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 : 100 mg/mL (260.82 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6082 mL	13.0412 mL	26.0824 mL
	5 mM	0.5216 mL	2.6082 mL	5.2165 mL
	10 mM	0.2608 mL	1.3041 mL	2.6082 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 (6.52 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.52 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.52 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

EAI045 is an allosteric and the fourth-generation inhibitor of mutant EGFR with IC_{50}s of 1.9, 0.019, 0.19 and 0.002 μM for EGFR, $EGFR^{L858R}$, $EGFR^{T790M}$ and $EGFR^{L858R/T790M}$ at 10 μM ATP, respectively.

IC_{50} & Target

EGFR	$EGFR^{L858R}$	$EGFR^{T790M}$	$EGFR^{L858R/T790M}$
1.9 μM (IC_{50})	0.019 μM (IC_{50})	0.19 μM (IC_{50})	0.002 μM (IC_{50})

In Vitro

EAI045 potently inhibits EGFR Y1173 phosphorylation in H1975 cells (EC_{50}=2 nM), but not in HaCaT cells. EAI045 is an

	inhibitor of the L858R/T790M mutant with 1000-fold selectivity versus wild type EGFR at 1 mM ATP. Profiling of EAI045 against a panel of 250 protein kinases reveals exquisite selectivity; no other kinases are inhibited by more than 20% at 1 μM EAI045[1]. EAI045 has high potency and selectivity for L858R/T790M mutation. In L858R/T790M-mutant NSCLC cell line H1975 cells, EAI045 decreases but does not completely abolish the EGFR autophosphorylation. In stably transfected NIH-3T3 cells harboring the L858R/T790M EGFR mutant, EAI045 shows the same activity. In L858R-mutant H3255 cells, EAI045 exhibits moderate activity. In the HaCaT cells, a keratinocyte cell line with wild-type EGFR, EAI045 does not show any activity of inhibiting EGFR phosphorylation. It confirms the selectivity of EAI045 for mutant EGFR[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In a genetically engineered mouse model of L858R/T790Mmutant-driven lung cancer , remarkable tumor regression is observed in L858R/T790M-mutant mice treated with the combination of EAI045 and cetuximab. No response is seen in those mice treated with EAI045 alone. The same effect is seen in both L858R/T790M/C797S- engineered Ba/F3 cells and in mice carrying the L858R/T790M/C797S tumor xenografts. These assays clearly show that EAI045 can overcome resistance from acquired T790M and C797S mutations[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	For the experiment studying the effect of EGF pre-treatment on EAI045 target modulation, H1975 cells are harvested and plated in 0.5% FBS/RPMI Pen/Strep. On the following day, cells are pre-treated with 0.5% FBS/RPMI media with or without 10 ng EGF/mL for 5 minutes. Compound is added and assay is carried out[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: Cetuximab is administrated at 1 mg/mouse every other day by intraperitoneal injection. The TL, TD and TLCS mice are monitored by MRI to quantify lung tumor burden before being assigned to various study treatment cohorts, which are non-blinded and not formally randomized. All treated mice had an equal initial tumor burden. MRI evaluation is repeated every 2 weeks during treatment. The animals are imaged with a rapid acquisition with relaxation enhancement sequence in the coronal and axial planes with a 1-mm slice thickness gating with respiratory rates. The tumor burden volumes are quantified[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Chromatogr Sci. 2020 Jun 5;58(6):562-568.

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REFERENCES

[1]. Jia Y, et al. Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors. Nature. 2016 Jun 2;534(7605):129-32.

[2]. Wang S, et al. EAI045: The fourth-generation EGFR inhibitor overcoming T790M and C797S resistance. Cancer Lett. 2017 Jan 28;385:51-54.

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