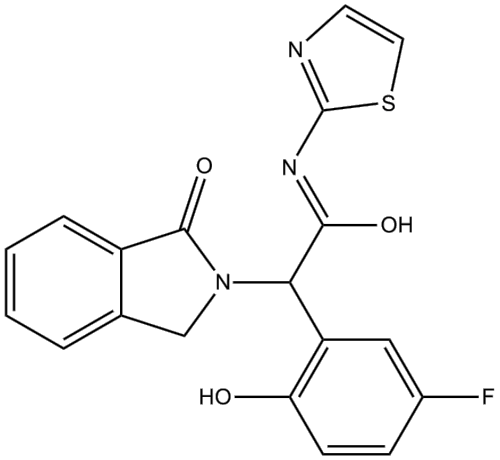
Product Data Sheet

Product Name: EAI045
Cat. No.: GC12281

Chemical Properties

Cas. No.	1942114-09-1		
Chemical Name	(Z)-2-(5-fluoro-2-hydroxyphenyl)-2-(1-oxoisoindolin-2-yl)-N-(thiazol-2-yl)acetimidic acid		
SMILES	FC1=CC(C(N2CC3=CC=CC=C3C2=O)/C(O)=N/C4=NC=CS4)=C(O)C=C1		
Formula	$C_{19}H_{14}FN_3O_3S$	M.Wt	383.4
Solubility	≥ 38.3mg/mL in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:

Cell lines EGFR mutant cell lines (H1975 and H3255); HaCaT cells

Product Data Sheet

Preparation method	This compound is soluble in DMSO. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.
Reacting condition	0-100 μM; 3 days
Applications	In H1975 cells, EAI045 potently decreased, but did not completely eliminate EGFR autophosphorylation and potently inhibited EGFR Y1173 phosphorylation with EC50 value of 2 nM. In the H1975 and H3255 cell lines, EAI045 (10 μM) showed no anti-proliferative effect. EAI045 inhibited proliferation of L858R/T790M and L858R mutant cells, but not the exon19del/T790M or parental Ba/F3 cells, suggesting the on-target, mutant selective activity.

Animal experiment [1]:

Animal models	EGFR-TL (L858R/T790M) and EGFR-TD (exon19del/T790M) mice
Dosage form	60 mg/kg daily by oral gavage; dissolved in 10% NMP (10% 1-methyl-2-pyrrolidinone: 90% PEG-300); 4-weeks
Application	In EGFR L858R/T790M-mutant lung cancer mouse model, EAI045 revealed a maximal plasma concentration of 0.57 μM, a half-life of 2.15 h, and oral bioavailability of 26% after dosing at 20 mg/kg. The combination of EAI045 (60 mg/kg) and cetuximab exhibited striking tumor regressions. EAI045 in combination with cetuximab effectively inhibited phosphorylation of EGFR and downstream signaling proteins.

Caution: Product has not been fully validated for medical applications. For research use only.
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Product Data Sheet

Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Jia Y, Yun CH, Park E et al. Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors. Nature. 2016 May 25;534(7605):129-32.

Background

EAI045 is an allosteric inhibitor that targets selected drug-resistant EGFR mutants but spares the wild-type receptor.

EGFR (epidermal growth factor receptor) is a cell-surface receptor tyrosine kinase. The receptor activation leads to dimerization and tyrosine autophosphorylation. It induces a cascade of downstream cellular responses such as modification in gene expression, cell proliferation and cytoskeletal rearrangement etc.

EAI1045 has an IC50 of 3 nM against the L858R/T790M mutant with a 1000-fold selectivity over wild-type EGFR at 1 mM ATP. In combination with 10 μg/ml cetuximab, EAI045 inhibited proliferation of EGFR (L858R/T790M) Ba/F3 cells with an IC50 of approximately 10nM.

In mice treated with EAI045 at 60 mg kg−1 by oral gavage once daily, combined treatment with cetuximab (1 mg intraperitoneally every other day) showed prominent tumour regressions, but these treated with EAI045 alone did not respond to the treatment.

Pharmacodynamic studies in exon19del/T790M and L858R/T790M/C797S mice indicated combined treatment of EAI045 with cetuximab effectively inhibited phosphorylation of EGFR and downstream signalling proteins in those mice, but not in mice with insensitive exon19del/T790M mutation.

Reference:

1. Jia Y, Yun CH, Park E et al.Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors. Nature. 2016 May 25;534(7605):129-32.