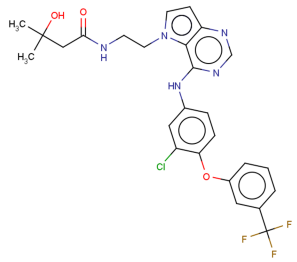
Data Sheet (Cat.No.T6039)

TargetMol
A DRUG SCREENING EXPERT

TAK-285

Chemical Properties



CAS No. : 871026-44-7

Formula: C26H25ClF3N5O3

Molecular Weight: 547.96

Appearance: no data available

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	TAK-285 is a novel dual HER2 and EGFR(HER1) inhibitor with IC50 of 17 nM and 23 nM, >10-fold selectivity for HER1/2 than HER4, less potent to MEK1/5, c-Met, Aurora B, Lck, CSK etc. Phase 1.
Targets(IC50)	EGFR,MEK,HER,Aurora Kinase
In vitro	Among the 34 kinases tested, TAK-285 only significantly inhibits HER4 with IC50 of 260 nM, slightly inhibits MEK1, MEK5, c-Met, Aurora B, Lck, CSK, and Lyn B with IC50 of 1.1 μM, 5.7 μM, 4.2 μM, 1.7 μM, 2.4 μM, 4.7 μM, and 5.2 μM, respectively, and displays no activity against other kinases with IC50 of >10 μM. TAK-285 shows significant growth inhibitory activity against BT-474 cells (HER2-overexpressing human breast cancer cell line) with GI50 of 17 nM. [1] Compared with SYR127063 a potent inhibitor of HER2, TAK-285 displays similar in vitro potency against HER2 and EGFR. Compared with the full cytoplasmic domains of the wild-type proteins, the mutations and shortened boundaries used for structure determination of HER2-KD and EGFR-KD do not significantly change the inhibitory activity (IC50) of TAK-285. TAK-285 binds to the inactive conformation of EGFR, and shows a similar binding mode with lapatinib in the active site. [2]
In vivo	The oral bioavailability of TAK-285 is 97.7% in rats and 72.2% in mice at a dose of 50 mg/kg. Oral administration of TAK-285 at 100 mg/kg twice daily for 14 days displays significant antitumor efficacy in the HER2-overexpressing BT-474 tumor xenograft mouse model with tumor/control (T/C) ratio of 29%, without affecting body weight. Similar to the BT-474 model, TAK-285 exhibits dose-dependent tumor growth inhibition of 4-1ST (HER2-overexpressing human gastric cancer tumor) xenografts in mice, with T/C of 44% and 11% at doses of 50 mg/kg and 100 mg/kg, twice daily, respectively, without significant body weight loss in mice. Furthermore, TAK-285 treatment induces dose-dependent growth inhibition of 4-1ST tumors in rats with T/C of 38% and 14% at doses of 6.25 mg/kg and 12.5 mg/kg, and, particularly noteworthy, tumor regression with T/C of -12% and -16% at doses of 25 mg/kg and 50 mg/kg, respectively. [1] After oral administration of TAK-285, a significant amount of TAK-285 is present in the brain of rats in pharmacologically active, unbound form (approximately 20% of its free plasma level), indicating that TAK-285 has a potential in the therapy of CNS malignancies/metastases. [3]
Kinase Assay	HER2 and EGFR kinase assay: The cytoplasmic domain (amino acids 676-1255) of human HER2 and the cytoplasmic domain (amino acids 669-1210) of human EGFR are

	expressed as N-terminal peptide (DYKDDDD)-tagged protein using a baculovirus expression system. The expressed HER2 kinase and EGFR kinase are purified by anti-FLAG M2 affinity gel. The EGFR and HER2 kinase assays are performed using radiolabeled [γ-32P]ATP in 96-well plates. The kinase reactions are performed in 50 mM Tris-HCl (pH 7.5), 5 mM MnCl2, 0.01% Tween 20, and 2 mM DTT containing 0.9 uCi of [γ-32P]ATP per reaction, 50 μM ATP, 5 ug/mL poly(Glu)-Tyr (4:1), and each purified cytoplasmic domain (0.25 μg/mL EGFR or HER2) in a total volume of 50 μL. To measure the IC50 value for enzyme inhibition, Increasing concentrations of TAK-285 are incubated with the enzyme for 5 minutes prior to the reaction at room temperature. The kinase reactions are initiated by adding ATP. After 10 minutes at room temperature, the reactions are stopped by the addition of 10% (final concentration) trichloroacetic acid. The γ-32P phosphorylated proteins are filtrated in a harvest plate with a cell harvester and washed free of [γ-32P]ATP with 3% phosphoric acid. The plates are dried followed by the addition of 25 μL of MicroScint0. The radioactivity is counted by a TopCount scintillation counter. IC50 values are calculated by nonlinear regression analysis of the percent inhibitions.
Cell Research	The cells are treated continuously with various concentrations of TAK-285 for 5 days. The live cell numbers are counted with a particle analyzer.(Only for Reference)

Solubility Information

Solubility	DMSO: 102 mg/mL (186.1 mM), Ethanol: 50 mg/mL (91.2 mM), H2O: <1 mg/mL, (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.825 mL	9.1248 mL	18.2495 mL
5 mM	0.365 mL	1.825 mL	3.6499 mL
10 mM	0.1825 mL	0.9125 mL	1.825 mL
50 mM	0.0365 mL	0.1825 mL	0.365 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Reference

Ishikawa T, et al. J Med Chem, 2011, 54(23), 8030-8050.
Aertgeerts K, et al. J Biol Chem, 2011, 286(21), 18756-18765.