Mubritinib (TAK 165)

Print

Catalog No.S2216

1 Reviews

Technical Data

Molecular Weight (MW)	468.47
Formula	$C_{25}H_{23}F_3N_4O_2$
CAS No.	366017-09-6

Storage	3 years -20°Cpowder
	6 months-80°Cin solvent
Synonyms	TAK 165, TAK165

Solubility (25°C) *	*In vitro*	DMSO	13 mg/mL (27.74 mM)
		Water	<1 mg/mL (<1 mM)
		Ethanol	<1 mg/mL (<1 mM)
	In vivo	1% DMSO/30% polyethylene glycol/1% Tween 80	5 mg/mL

* <1 mg/ml means slightly soluble or insoluble.
* Please note that Selleck tests the solubility of all compounds in-house, and the actual solubility may differ slightly from published values. This is normal and is due to slight batch-to-batch variations.

Chemical Name	(E)-1-(4-(4-((2-(4-(trifluoromethyl)styryl)oxazol-4-yl)methoxy)phenyl)butyl)-1H-1,2,3-triazole

Preparing Stock Solutions

	1 mg	5 mg	10 mg
1 mM	2.1346 mL	10.6730 mL	21.3461 mL
5 mM	0.4269 mL	2.1346 mL	4.2692 mL
10 mM	0.2135 mL	1.0673 mL	2.1346 mL

50 mM	-	-	-

Biological Activity

Description	Mubritinib (TAK-165) is a potent inhibitor of **HER2/ErbB2** with **IC50** of 6 nM in BT-474 cell; no activity to EGFR, FGFR, PDGFR, JAK1, Src and Blk in BT-474 cell line. Phase 1.					
Targets	ErbB2					
IC50	6 nM [1]					
In vitro	Mubritinib displays > 4000-fold selectivity over other tyrosine kinases, such as EGFR, FGFR, PDGFR, Jak1, Src and Blk. Mubritinib even at low concentration of 0.1 μM significantly blocks HER2 phosphorylation, leading to the downregulation of PI3K-Akt and MAPK pathway in cell line BT474 with high level of HER2. Mubritinib not only exhibits highly potent antiproliferative effect in ErbB2-overexpressing cancer cell line BT474 with an IC50 of 5 nM, but also displays marked antiproliferative effects in cell lines with HER2 expressed weakly with IC50 of 53 nM, 90 nM and 91 nM for LNCaP, LN-REC4 and T24, respectively. Mubritinib displays no inhibitory activities against PC-3 cells with HER2 expressed very faintly with IC50 of 4.62 μM, as well as EGFR-overexpressing HT1376 and ACHN cell lines with IC50 of >25 μM. [1]					
In vivo	Mubritinib significantly inhibits LN-REC4 xenograft with treatment/control tumor volume ratio of 26.5%. Although ineffective to inhibit the growth of UMUC-3 and ACHN cells in vitro (IC50s of 1.812 and >25 μM, respectively), oral administration of Mubritinib (10 or 20 mg/kg per day) significantly inhibits the growth of UMUC-3 and ACHN xenografts with treatment/control tumor volume ratio of 22.9% and 26%, respectively, as compared with Herceptin (20 mg/kg) which is ineffective to UMUC-3 tumor growth. [1]					
Features						

Protocol (Only for Reference)

Kinase Assay: [1]

Inhibition of HER2/erbB2 tyrosine kinase activity	BT-474 cells are seeded on 24-well plates and cultured overnight. Mubritinib is then added at various concentrations. After incubation for 2 hours, the cells are harvested directly into sodium dodecyl sulfate (SDS)-sample buffer (200 μL). Aliquots containing equal amounts of total cell extract are run on 7.5% to 15% gradient SDS–polyacrylamide gel electrophoresis (PAGE). Following electrophoresis, proteins are transferred onto a polyvinylidene fluoride (PVDF) membrane, for western blot analysis using a relevant primary antibody. Detection of protein is accomplished by an enhanced chemiluminescent (ECL) detection method. The extent of tyrosine phosphorylation of HER2/erbB2 is measured by the LAS-1000 plus lumino-image analyser. The concentration of Mubritinib that inhibits HER2/erbB2 phosphorylation by 50% (IC50) is calculated

	from a dose–response curve generated by least-squares linear regression of the response using SAS software.

Cell Assay: [1]

Cell lines	BT474, HT1376, UMUC-3, T24, ACHN, DU-145, PC-3, LN-REC4, and LNCaP cells
Concentrations	Dissolved in DMSO, final concentrations ~50 mM
Incubation Time	72 hours
Method	Cells are seeded into 6-well plates and cultured overnight. Mubritinib is then added at various concentrations, and the cells are treated continuously for 72 hours. After the incubation period, cells are counted for the measurement of antiproliferative activity.

Animal Study: [1]

Animal Models	Athymic nude mice (BALB/c nu/nμ) and SCID mice (C.B.-17 Scid/Scid) are implanted subcutaneously with UMUC-3, LN-REC4 or ACHN cells
Formulation	Dissolved in DMOS and diluted in saline
Dosages	10 or 20 mg/kg/day
Administration	Orally twice daily

Conversion of different model animals based on BSA (Value based on data from FDA Draft Guidelines)

Species	Mouse	Rat	Rabbit	Guinea pig	Hamster	Dog
Weight (kg)	0.02	0.15	1.8	0.4	0.08	10
Body Surface Area (m^2)	0.007	0.025	0.15	0.05	0.02	0.5
K_m factor	3	6	12	8	5	20

Animal A (mg/kg) = Animal B (mg/kg) multiplied by $\frac{\textbf{Animal B } K_m}{\textbf{Animal A } K_m}$

For example, to modify the dose of resveratrol used for a mouse (22.4 mg/kg) to a dose based on the BSA for a rat, multiply 22.4 mg/kg by the K_m factor for a mouse and then divide by the K_m factor for a rat. This calculation results in a rat equivalent dose for resveratrol of 11.2 mg/kg.

Rat dose (mg/kg) = mouse dose (22.4 mg/kg) × mouse K_m(3) = 11.2 mg/kg

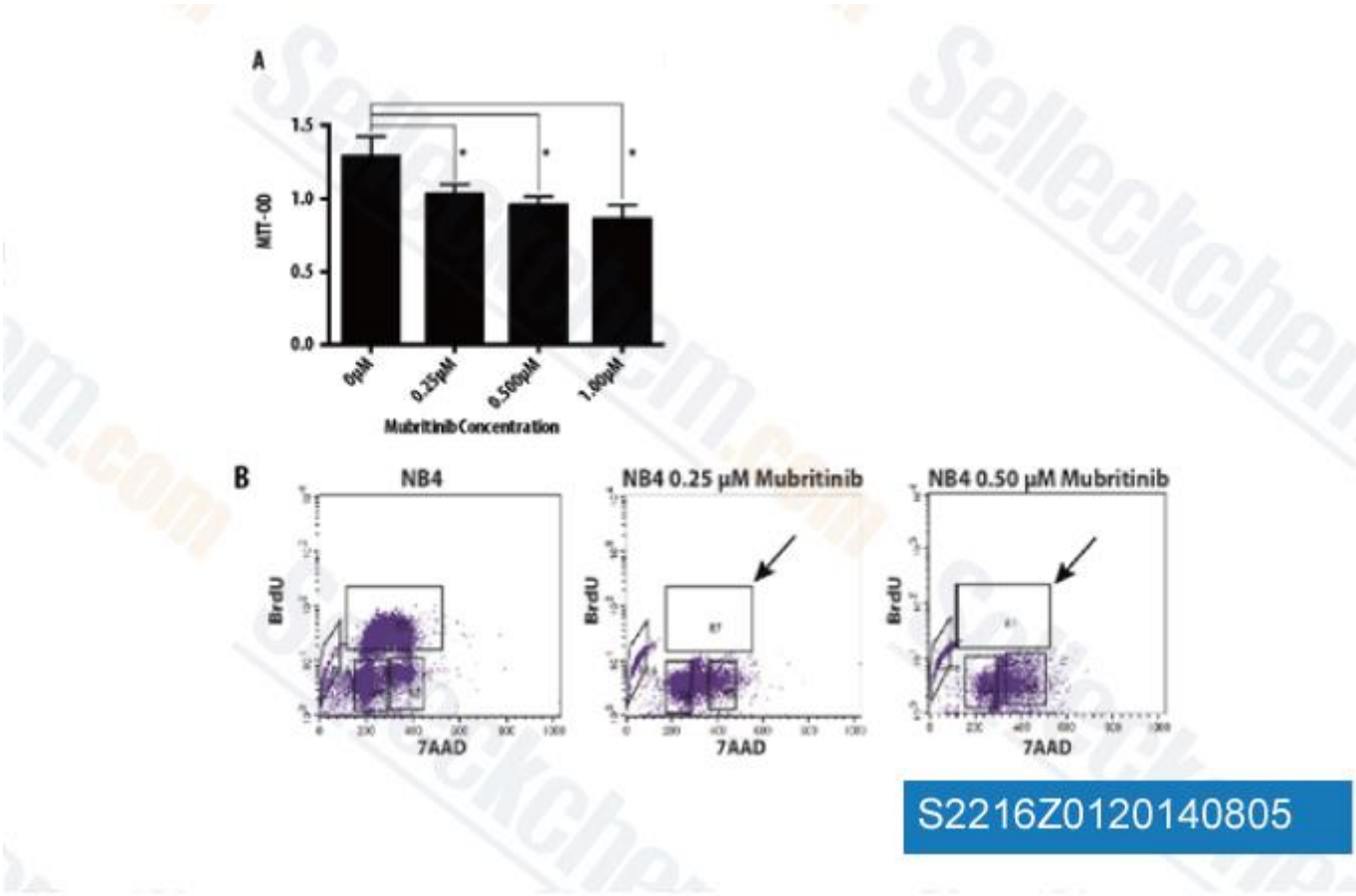
rat K_m(6)

1

References

[1] Nagasawa J, et al. Int J Urol, 2006, 13(5), 587-592.

Customer Product Validation



Data from [**Leuk Res**, 2014, 38(3), 402-10]
Mubritinib (TAK 165) purchased from **Selleck**

(A) Cell proliferationanalysis of NB4 cells 24 h post-Mubritinib treatments(0–1 uM) as measured by MTT proliferation assay. (B) Representative images of cell cycle progression analysis of NB4 cells 24 h post 0.25 uM and 0.5 uM Mubritinib Treatment measured by BrdU flow cytometry.

Mubritinib (TAK 165) has been referenced in 4 publications.

- The HDAC inhibitor, MPT0E028, enhances erlotinib-induced cell death in EGFR-TKI-resistant NSCLC cells. [Chen MC, et al. Cell Death Dis, 2013, 4:e810]

PubMed: 24052078

- A guide to picking the most selective kinase inhibitor tool compounds for pharmacological validation of drug targets. [Uitdehaag JC, et al. Br J Pharmacol, 2012, 166(3):858-76]

PubMed: 22250956

- miR-125a regulates cell cycle, proliferation, and apoptosis by targeting the ErbB pathway in acute myeloid leukemia [Ufkin ML, et al. Leuk Res, 2014, 38(3):402-10]

PubMed: 24484870

- Establishment and Characterization of a Singaporean Chinese Lung Adenocarcinoma Cell Line with Four Copies of the Epidermal Growth Factor Receptor Gene [Choong ML, et al. Biores Open Access, 2014, 3(4):176-82]

PubMed: 25126481

PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.