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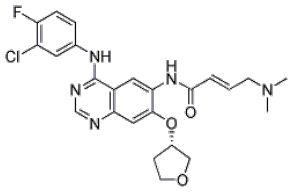
Afatinib (BIBW2992) Datasheet

Technical Data

Molecular Weight (MW)	485.94
Formula	$C_{24}H_{25}ClFN_5O_3$
CAS No.	439081-18-2, 936631-70-8 (Maleic acid), 1254955-21-9 (XHCl)
Synonyms	Tomtovok

Solubility (25°C)	DMSO 97 mg/mL		
	Water <1 mg/mL		
	Ethanol 15 mg/mL		
Storage	2 years	-20°C	Powder
	2 weeks	4°C	in DMSO
	6 months	-80°C	in DMSO

Afatinib (BIBW2992) Chemical Structure



Biological Activity

Description	BIBW2992 (Afatinib, Tomtovok, Tovok) irreversibly inhibits EGFR/HER2 including **$EGFR^{wt}$**, **$EGFR^{L858R}$**, $EGFR^{L858R/T790M}$ and HER2 with **IC50** of 0.5 nM, 0.4 nM, 10 nM and 14 nM, respectively.					
Targets	$EGFR^{wt}$	$EGFR^{L858R}$	$EGFR^{L858R/T790M}$	HER2		
IC50	0.5 nM	0.4 nM	10 nM	14 nM [1]		
In vitro	BIBW2992 shows potent activity against both wild-type and mutant forms of EGFR and HER2. It is similar to Gefitinib in potency against L858R EGFR, but about 100-fold more active against the Gefitinib resistant L858R-T790M EGFR double mutant. BIBW2992 exhibits potent effects on both EGFR and HER2 phosphorylation in vivo. It compares favorably to reference compounds (such as Lapatinib et al.) in all cell types tested, such as human epidermoid carcinoma cell line A431 expressing wt EGFR, murine NIH-3T3 cells transfected with wt HER2, as well as breast cancer cell line BT-474 and gastric cancer cell line NCI-N87, which express endogenous HER2. [1]					
In vivo	Daily oral administration of BIBW2992 at 20 mg/kg for 25 days results in dramatic tumor regression with a cumulative treated/control tumor volume ratio (T/C ratio) of 2%. Reduced phosphorylation of EGFR and AKT is confirmed by immunohistochemical staining of tissue sections. Therefore, like lapatinib and neratinib, BIBW2992 is a next generation tyrosine kinase inhibitor (TKI) that inhibits human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases irreversibly. BIBW2992 is not only active against EGFR mutations targeted by first generation TKIs like Erlotinib or Gefitinib, but also against those insensitive to these standard therapies. [1]					
Clinical Trials	A Phase II clinical trial of BIBW2992 for the treatment of cancer has been terminated.					
Features						

Protocol (Only for Reference)

Kinase Assay: [1]

In vitro kinase activity assays	The wild type tyrosine kinase domain of the human EGFR as well as that of the EGFR L858R/T790M double mutant are fused to Glutathione-S-transferase (GST), and extracted. Enzyme activity is then assayed in the presence of the inhibitor BIBW2992, serially diluted in 50% DMSO. A random polymer pEY (4:1) is used as substrate and biotinylated pEY (bio-pEY) is added as a tracer substrate. The kinase domain of HER2 is cloned using the baculovirus system and extracted similarly to that of EGFR kinase. Details of assays for EGFR, HER2, SRC, BIRK and VEGFR2 kinase activity are available in Supplementary information.

Cell Assay: [1]

Cell Lines	NSCLC cells
Concentrations	0-10 μM
Incubation Time	1 hour
Methods	1×10^4 NSCLC cells are transferred into each well of a 96-well plate and cultured overnight in serum-free media for the EGFR phosphorylation assay. After addition of BIBW2992 on the next day, the plates are incubated at 37 °C for 1 hour. EGF-stimulation is done using 100 ng/mL for 10 min at room temperature. Cells are washed with ice cold PBS, extracted with 120 μL HEPEX buffer per well and shaken at room temperature for 1 hour. In all 2×10^4 cells per well is used for the HER2 phosphorylation assay. Streptavidin precoated plates are coated with anti-EGFR-biotin at 1:100 dilution in blocking buffer and c-erb2/HER2 oncoprotein Ab-5(Clone N24)-Biotin. Cell extracts is then transferred to the antibody-coated wells and incubated at room temperature for 1 hour. Extinction was measured at 450 nm.

Animal Study: [1]

Animal Models	Athymic NMRI-nu/nu female mice
Formulation	In 0.5% methocellulose-0.4% polysorbate-80 (Tween 80)
Doses	20 mg/kg
Administration	Oral administration

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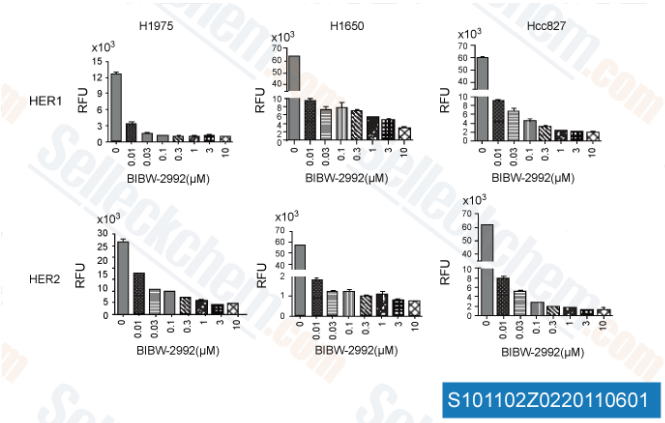
References

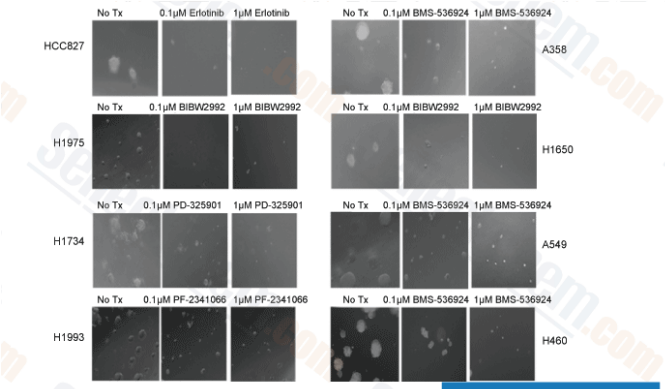
[1] Li D, et al. Oncogene, 2008, 27(34), 4702-4711.

Customer Reviews



S101102Z0220110601

Data from [**Int J Proteomics** , 2011.June, 2011:Article ID 215496]
Afatinib (BIBW2992) purchased from **Selleck**
Inhibition of signaling pathway activation in lung tumor cell lines by kinase inhibitors. Lung tumor cells were cultured in 10% FBS until reaching ~80% confluence and then the cells were starved in serum-free medium for overnight, followed by 4-hour treatment with the inhibitors. Cell lysates were then prepared and used for determination of the pathway activation signals by the CEER assay.



S101102Y0320110601

Data from [**Int J Proteomics** , 2011.June, 2011:Article ID 215496]
Afatinib (BIBW2992) purchased from **Selleck**
Inhibition of anchorage-independent growth of lung tumor cell lines by selected inhibitors. Each selected cell line was treated with the indicated inhibitor at 0.1 μM and 1 μM concentrations for two weeks and cell colony size formation was scored under the Nikon inverted-phase microscope.

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