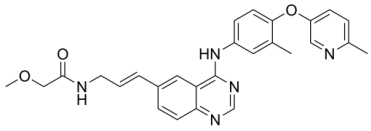
Data Sheet

Product Name:	CP-724714
Cat. No.:	CS-0262
CAS No.:	383432-38-0
Molecular Formula:	$C_{27}H_{27}N_5O_3$
Molecular Weight:	469.55
Target:	Apoptosis; EGFR
Pathway:	Apoptosis; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 50 mg/mL



BIOLOGICAL ACTIVITY:

CP-724714 is a potent, selective and orally active **ErbB2 (HER2)** tyrosine kinase inhibitor, with an **IC_{50}** of 10 nM. CP-724714 displays a marked selectivity against EGFR kinase (IC_{50}=6400 nM). CP-724714 potently inhibits ErbB2 receptor autophosphorylation in intact cells. Antitumor activities[1][2]. ***In Vitro:*** CP-724714 is >1,000-fold less potent for insulin receptor, insulin-like growth factor-I receptor, platelet-derived growth factor β, vascular endothelial growth factor 2, Abl, Src, c-Met, JNK-2, JNK-3, ZAP-70, Cdk-2, and Cdk-5[1].
CP-724714 potently reduces the EGF-induced autophosphorylation of the chimera containing the erbB2 kinase domain at a concentration as low as 50 nmol/L (IC_{50}=32 nM) but is markedly less potent against EGFR[1].
CP-724714 (1 μM; 24 hours) induces G1 cell cycle block in vitro in erbB2-overexpressing BT-474 human breast carcinoma cells[1]. ***In Vivo:*** CP-724714 (3.25-100 mg/kg; p.o.; 0.5-8 hours) results in a concentration-dependent reduction of ErbB2 receptor phosphorylation[1].
CP-724714 (6.25-100 mg/kg; p.o.; q.d; for 8 to 40 day) inhibits FRE-erbB2 xenograft growth[1].
CP-724714 (Athymic, female FRE-erbB2 xenograft-bearing mice; 30 or 100 mg/kg; p.o.) treatments results in a time- and dose-dependent induction of apoptosis, which was evident as early as 4 to 8 h after dosing. Approximately 75% more tumor cells exhibited apoptotic changes in the 100 mg/kg treatment group compared with vehicle control group at 8 h after dosing. CP-724714 induces regression of BT-474 tumors and significant inhibition in a number of other human tumor xenografts. Additionally, CP-724714 showed a favorable nonclinical toxicity profile with no apparent effects on cardiac tissue[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] Cells were seeded in duplicate at 5,000 to 10,000 per well in 24-well plates. The day after plating, CP-724,714 was added by titrating over six or more dilutions from 10 μM down. Control wells without drug were seeded as well. Cells were grown for 6 to 7 days, at which time surviving cells were counted. After trypsinization, cells were placed in isotone solution and counted immediately using a Coulter Z2 particle counter. Growth inhibition was calculated [(1- experimental value / control value) × 100] for each concentration. Dose-response curves were repeated at least twice and averaged. IC50 values were calculated using Calcusyn Software. Animal administration [1] FRE-erbB2 xenograft-bearing mice were treated with vehicle (0.5% methylcellulose) or CP-724,714 (3.125, 6.25, 12.5, 25, 50, and 100 mg/kg, p.o., in 0.5% methylcellulose) and tumors and plasma were isolated at 1 h after dosing. Tumors were homogenized in ice-cold lysis buffer [50 mM HEPES (pH 7.4), 150 mM NaCl, 1.5 mM MgCl2, 1 mM EDTA,1% Glycerol, 1% Triton X-100, 1.6 mM Na3VO4, 50 mM NaF, Protease Inhibitor Cocktail] at 1 mL buffer/100 mg of tumor wet weight. ErbB2 phosphorylation status was determined using a neu-coated ELISA plate to capture the receptor and the plate is probed with a horseradish peroxidase-conjugated anti-phosphotyrosine antibody (PY99). Inhibition of erbB2 phosphorylation was measured as the decrease of ELISA signal relative to the vehicle-treated control tumors.

References:

[1]. Jani JP, et al. Discovery and pharmacologic characterization of CP-724,714, a selective ErbB2 tyrosine kinase inhibitor. Cancer Res, 2007, 67(20), 9887-9893.

[2]. Feng B, et al. Role of hepatic transporters in the disposition and hepatotoxicity of a HER2 tyrosine kinase inhibitor CP-724,714. Toxicol Sci, 2009, 108(2), 492-500.

CAIndexNames:

Acetamide, 2-methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]-

SMILES:

O=C(COC)NC/C=C/C1=CC2=C(N=CN=C2C=C1)NC3=CC=C(C(C)=C3)OC4=CC=C(N=C4)C

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