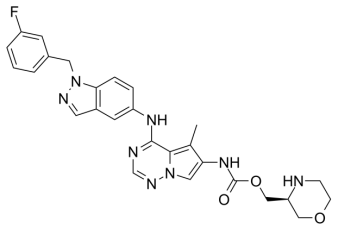
BMS-599626

Cat. No.:	HY-10251
CAS No.:	714971-09-2
Molecular Formula:	$C_{27}H_{27}FN_8O_3$
Molecular Weight:	530.55
Target:	EGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

BMS-599626 (AC480) is a selective and orally bioavailable HER1 and HER2 inhibitor, with IC_{50}s of 20 and 30 nM, respectively. BMS-599626 displays ~8-fold less potent to HER4 (IC_{50}=190 nM), >100-fold to VEGFR2, c-Kit, Lck, MEK. BMS-599626 inhibits tumor cell proliferation, and has potential to increase tumor response to radiotherapy[1][2].

In Vitro

BMS-599626 inhibits the proliferation of tumor cells that are dependent on HER1/HER2 signaling. BMS-599626 (0.03-8 μM; 1 huors) results in the inhibition of receptor autophosphorylation, as well as MAPK phosphorylation, with IC_{50}s of 0.3 and 0.22 μM, respectively, in Sal2 cells which express a CD8HER2 fusion protein[1].

BMS-599626 abrogates HER1 and HER2 signaling and inhibited the proliferation of tumor cell lines that are dependent on these receptors, with IC_{50} in the range of 0.24 to 1 μM.In GEO cells, HER1 phosphorylation is stimulated by treatment with EGF and is inhibited by BMS-599626 (IC_{50}=0. 75 μM).There is also nearly complete inhibition of EGF-dependent MAPK (0. 8 μ M) but only partial inhibition of AKT signaling.The latter likely reflects the activation of AKT by multiple upstream signals.Treatment of N87 cells with BMS-599626 leads to the inhibition of HER2 (0. 38 μM), which is expressed to a high level because of gene amplification, as well as MAPK and AKT phosphorylation (0.35 μM for both)[1].

At the molecular level, in HN-5 cells the agent inhibited the expression of pEGFR, pHER2, cyclins D and E, pRb, pAkt, pMAPK, pCDK1 and 2, CDK 6, and Ku70 proteins. The drug also induced accumulation of cells in the G1 cell cycle phase, inhibited cell growth, enhanced radiosensitivity, and prolonged the presence of γ-H AX foci up to 24 h after radiation[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

BMS-599626 (60-240 mg/kg; p.o.; daily for 14 days) results in a dose-dependent inhibition of Sal2 tumor growth[1].

BMS599626 treatment results in the inhibition of GEO xenograft tumor growth when given once daily for 14 days. In addition to efficacy in the Sal2, GEO, and KPL4 models, BMS-599626 has similar antitumor activity in other HER2 amplified xenograft models including the BT474 breast and N87 gastric tumors, as well as other HER1-overexpressing non-small-cell lung tumors (A549 and L2987)[1].

BMS599626 given before and during irradiation improved the radioresponse of HN5 tumors in vivo[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Athymic female nude mice (nu/nu mice, Sal2 tumor model)[1]
Dosage:	60, 120, 240 mg/kg
Administration:	Oral; daily for 14 days
Result:	Resulted in a dose-dependent inhibition of Sal2 tumor growth.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Life Sci. 2021 Dec 16;289:120231.

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REFERENCES

[1]. Wong TW, et al. Preclinical antitumor activity of BMS-599626, a pan-HER kinase inhibitor that inhibits HER1/HER2 homodimer and heterodimer signaling. Clin Cancer Res. 2006 Oct 15;12(20 Pt 1):6186-93.

[2]. Torres MA, et al. AC480, formerly BMS-599626, a pan Her inhibitor, enhances radiosensitivity and radioresponse of head and neck squamous cell carcinoma cells in vitro and in vivo. Invest New Drugs. 2011 Aug;29(4):554-61.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA