Amuvatinib hydrochloride

Cat. No.: HY-10206A

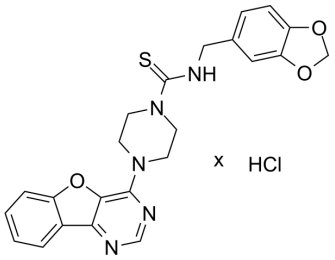
CAS No.: 1055986-67-8

Molecular Formula: $C_{23}H_{21}N_5O_3S.xHCl$

Target: c-Kit; PDGFR; RAD51; FLT3; c-Met/HGFR; RET

Pathway: Protein Tyrosine Kinase/RTK; Cell Cycle/DNA Damage

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

Amuvatinib hydrochloride (MP470 hydrochloride) is an orally bioavailable multi-targeted tyrosine kinase inhibitor with potent activity against mutant c-Kit, PDGFRα, Flt3, c-Met and c-Ret. Amuvatinib hydrochloride (MP470 hydrochloride) is also a DNA repair suppressor through suppression of DNA repair protein RAD51, thereby disrupting DNA damage repair[1][2][3]. Antineoplastic activity[4].

IC_{50} & Target

$PDGFR\alpha^{V561D}$ 40 nM (IC_{50})	$PDGFR\alpha^{D842V}$ 81 nM (IC_{50})	$c\text{-}Kit^{D816H}$ 10 nM (IC_{50})	$c\text{-}Kit^{V560G}$ 34 nM (IC_{50})
$c\text{-}Kit^{V654A}$ 127 nM (IC_{50})	$c\text{-}Kit^{D816V}$ 950 nM (IC_{50})		

In Vitro

Amuvatinib (MP470) inhibits c-Kit (D816V), c-Kit (D816H), c-Kit (V560G), c-Kit (V654A), PDGFRα (D842V), and PDGFRα (V561D) with IC_{50}s of 950 nM, 10 nM, 34 nM, 127 nM, 81 nM, and 40 nM, respectively[4].

Amuvatinib (MP470), a novel receptor tyrosine kinase (RTK) inhibitor has shown growth inhibitory activity against a variety of cancer cell lines. Amuvatinib (0.1-10 μM, 4 days incubation) is effective on LNCaP and PC-3 cells with IC_{50}s of ~4 μM and 8 μM, respectively. When Erlotinib (10 μM) is combined with varying doses of Amuvatinib, the IC_{50} of Amuvatinib decreases to 2 μM on LNCaP cells[5].

Akt activity (as measured by phosphorylation on Ser473) is significantly reduced by 10 μM Amuvatinib (treated for 30 hours) alone but is not reduced by Erlotinib or Imatinib Mesylate (IM). Moreover, Amuvatinib plus Erlotinib completely abolished Akt phosphorylation in LNCaP cells with an unchanged total protein level of Akt[5].

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

Cell Viability Assay[2]

Cell Line:	Prostate cancer cell lines (LNCaP, PC-3 and DU-145)
Concentration:	0.1-10 μM
Incubation Time:	4 days
Result:	The IC_{50} for LNCaP and PC-3 was ~4 μM and 8 μM, respectively. Had only a modest effect on the viability of DU-145 cells.

Western Blot Analysis[2]

Cell Line:	LNCaP cells
Concentration:	2,5,10 μM
Incubation Time:	30 hours
Result:	Akt activity (as measured by phosphorylation on Ser473) was significantly reduced at 10 μ M.

In Vivo

Four LNCaP xenograft arms each with 12 mice are dosed intraperitoneally with DMSO (control) or Erlotinib 80 mg/kg or Amuvatinib (MP470) 50 mg/kg or Erlotinib 80 mg/kg plus Amuvatinib 50 mg/kg daily for 2 weeks and then observed for a further 11 days. Individual therapy with Amuvatinib or Erlotinib shows modest tumor growth inhibition (TGI), while Amuvatinib plus Erlotinib has a marked effect on TGI (45-65%). However, due to the high doses of Amuvatinib used, only five or one mouse remained alive in the combination arm at the end of treatment or at the end of the study, respectively. Therefore the Amuvatinib dose is reduced to 10 mg/kg or 20 mg/kg for the combination treatment. TGI in the group receiving 10 mg/kg Amuvatinib+80 mg/kg Erlotinib is not significantly different from the control group. However, mice receiving 20 mg/kg Amuvatinib+80 mg/kg Erlotinib have a significant TGI compared to the control group (p=0.01)[5].

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Animal Model:	Forty eight 6-7 week-old SCID male mice with LNCaP xenograft model[2]
Dosage:	10 mg/kg and 20 mg/kg, 50 mg/kg
Administration:	Administered i.p. daily from days 1 to 24
Result:	Individual therapy showed modest tumor growth inhibition (TGI), while combination had a marked effect on TGI (45-65%).

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Sci Signal. 2019 Jul 16;12(590). pii: eaav7259.
- Sci Rep. 2021 Jan 14;11(1):1333.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Choy G, et al. Safety, tolerability, and pharmacokinetics of amuvatinib from three phase 1 clinical studies in healthy volunteers. Cancer Chemother Pharmacol. 2012 Jul;70(1):183-90.

[2]. Baxter PA, et al. Plasma and cerebrospinal fluid pharmacokinetics of MP470 in non-human primates. Cancer Chemother Pharmacol. 2011 Apr;67(4):809-12.

[3]. Tibes R, et al. A phase I, first-in-human dose-escalation study of amuvatinib, a multi-targeted tyrosine kinase inhibitor, in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2013 Feb;71(2):463-71.

[4]. David J. Bearss, et al. Pharmaceutical formulations comprising salts of a protein kinase inhibitor and methods of using same. US20080226747A1.

[5]. Qi W, et al. MP470, a novel receptor tyrosine kinase inhibitor, in combination with Erlotinib inhibits the HER family/PI3K/Akt pathway and tumor growth in prostate

cancer. BMC Cancer. 2009 May 11;9:142.

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