Agerafenib hydrochloride

Cat. No.: HY-15199

CAS No.: 1227678-26-3

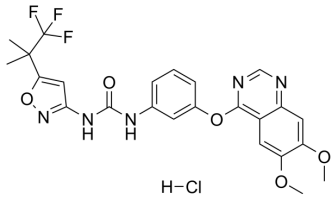
Molecular Formula: $C_{24}H_{23}ClF_3N_5O_5$

Molecular Weight: 553.92

Target: Raf

Pathway: MAPK/ERK Pathway

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



BIOLOGICAL ACTIVITY

Description	Agerafenib hydrochloride is a highly potent and orally efficacious inhibitor of $BRAF^{V600E}$ with a K_d of 14 nM.			
IC_{50} & Target	$BRaf^{V600E}$ 14 nM (Kd)	Braf 36 nM (Kd)	CRAF 39 nM (Kd)	c-Kit 2 nM (Kd)
	Ret 2 nM (Kd)	LCK 2 nM (Kd)	Abl-1 3 nM (Kd)	VEGFR-2 8 nM (Kd)
	CSF-1R 9 nM (Kd)	EPHA2 14 nM (Kd)	EGFR 22 nM (Kd)	c-Met 513 nM (Kd)
	JAK-2 4700 nM (Kd)	MEK-1 7100 nM (Kd)	MEK-2 8300 nM (Kd)	

In Vitro

Agerafenib (CEP-32496) exhibits high potency against several $BRAF^{V600E}$-dependent cell lines and selective cytotoxicity for tumor cell lines expressing mutant $BRAF^{V600E}$ versus those containing wild-type BRAF. Agerafenib (CEP-32496) exhibits potent binding ($BRAF^{V600E}$ K_d=14 nM) and cellular activity (pMEK IC_{50}=82 nM and A375 proliferation IC_{50}=78 nM), with activity in the proliferation assay. CEP-32496 also exhibits a favorable CYP450 inhibition profile, with measured IC_{50} values greater than 10 μM versus the CYP1A2, CYP2C9, CYP2D6, and CYP3A4 isoforms and an IC_{50}=3.4 μM versus CYP2C19[1].

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

In Vivo

Oral administration of Agerafenib (CEP-32496) to Colo-205 tumor xenograft-bearing mice results in significant inhibition of pMEK in tumor cell lysates. For instance, a single 30 mg/kg (po) dose of Agerafenib (CEP-32496) leads to a 50 and 75% inhibition of normalized pMEK in tumor lysates at the 2 and 6 h postdose time point, respectively ($p<0.03$), while a 55 mg/kg (po) dose resulted in a 75% to 57% ($p<0.03$) inhibition of pMEK at 2 through 10 h post administration, with normalization to baseline by 24 h. Agerafenib (CEP-32496) exhibits an exceptional PK profile in mouse, dog, and cynomolgus monkey. Administration of Agerafenib (CEP-32496) to beagle dogs (single dose of 1 mg/kg iv and 10 mg/kg po) results in low clearance (CL=5.0 (mL/min)/kg) and excellent bioavailability (%F=100). Similarly, in cynomolgus monkey, the administration of Agerafenib (CEP-32496) (single dose of 1 mg/kg iv and 10 mg/kg po) leads to high oral exposure due to low clearance (CL=6.7 mL/min/kg) and excellent bioavailability (%F=100)[1].

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

PROTOCOL

Cell Assay [1]	A375 cells are seeded at 10,000 cells per well in DMEM with 10% fetal calf serum and allowed to attach. The cells are washed with PBS and switched to DMEM with 0.5% of serum and incubated overnight. The test compounds (e.g., Agerafenib (CEP-32496); 10 μM) are then added at various concentrations with a final DMSO concentration of 0.5% and incubated for 72 h. At the end of incubation, a Cell Titer Blue is added per instructions, and incubation is continued for 3 h. Remaining viable cells are quantified by measuring the strength of the fluorescence signal using SoftMax Pro (excitation at 560 nm and emission at 590 nm). IC_{50} values are derived using a 9-point curve and are presented as mean values from experiments performed in duplicate[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Six to eight week old athymic nu/nu nude mice (20-25 g) are inoculated subcutaneously with Colo-205 tumor cells (1×10^6 /mouse) in the right flank. Upon reaching an average tumor volume of 150-200 mm^3 (10-12 days post implantation), animals are randomized into treatment groups (n=10 mice/group). Each group is dosed orally for 14 days with either vehicle only (22% HPβCD) or with Agerafenib (CEP-32496) at 10, 30, or 100 mg/kg twice daily (BID), and each dose of drug is given in a volume of 0.1 mL per 20 g of body weight, adjusted for the body weight of the animal. Tumor volumes are measured three times weekly using vernier calipers, and volumes are calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Nat Biomed Eng. 2018 Aug;2(8):578-588.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Patent. US20220098204A1.
- Patent. US20210379056A1.

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REFERENCES

[1]. Rowbottom MW, et al. Identification of 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea hydrochloride (CEP-32496), a highly potent and orally efficacious inhibitor of V-RAF murine sarcoma viral oncogene homologue B1 (BRAF) V600E.

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