Agerafenib

Cat. No.: HY-15200

CAS No.: 1188910-76-0

Molecular Formula: $C_{24}H_{22}F_3N_5O_5$

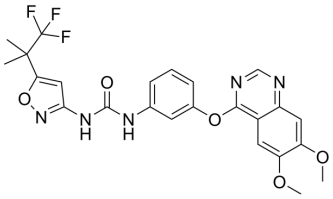
Molecular Weight: 517.46

Target: Raf

Pathway: MAPK/ERK Pathway

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (96.63 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9325 mL	9.6626 mL	19.3252 mL
5 mM	0.3865 mL	1.9325 mL	3.8650 mL
10 mM	0.1933 mL	0.9663 mL	1.9325 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.83 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.83 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.83 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Agerafenib (CEP-32496; RXDX-105) 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 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. Agerafenib 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[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 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 exhibits an exceptional PK profile in mouse, dog, and cynomolgus monkey. Administration of Agerafenib 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 (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].

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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; 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].

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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 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].

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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.

- J Med Virol. 2022 Oct 17.
- Patent. US20220098204A1.

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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.

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