Spebrutinib

Cat. No.: HY-18012

CAS No.: 1202757-89-8

Molecular Formula: $C_{22}H_{22}FN_5O_3$

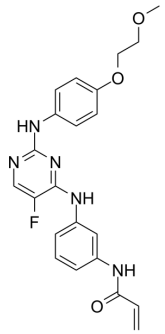
Molecular Weight: 423.44

Target: Btk

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 45 mg/mL (106.27 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Mass / Solvent / Concentration	1 mg	5 mg	10 mg
1 mM	2.3616 mL	11.8080 mL	23.6161 mL
5 mM	0.4723 mL	2.3616 mL	4.7232 mL
10 mM	0.2362 mL	1.1808 mL	2.3616 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 (5.90 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Spebrutinib (AVL-292; CC-292) is a covalent, orally active, and highly selective with an IC_{50} of 0.5 nM.

IC_{50} & Target

IC50: <0.5 nM (Btk)[1]

In Vitro

Spebrutinib (CC-292) is a covalent, highly selective, orally active inhibitor of Btk with IC_{50} value of 0.5 nM. Spebrutinib also less potently inhibits Yes, c-Src, Brk, Lyn, and Fyn with IC_{50}s of 723 nM, 1.729 μM, 2.43 μM, 4.4 μM, and 7.15 μM, rspectively. Extensive analysis has revealed that the EC_{50} of Btk occupancy from a Spebrutinib dose-response in Ramos cells (EC_{50}=6 nM) correlated directly with the cellular EC_{50} of Btk kinase inhibition with Spebrutinib (EC_{50}=8 nM). Furthermore, the concentration at which Spebrutinib inhibits 90% of Btk activity in Ramos cells is 35 nM while the concentration of

Spebrutinib required for 90% occupancy of Btk is 39 nM[1].

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

PROTOCOL

Cell Assay [1]

Cells are incubated in serum-free RPMI media for 1-1.5 hours. Isolated human B cells are incubated with Spebrutinib at a final concentration of 0.001, 0.01, 0.1 and 1 μM. Ramos cells are incubated with 0.1 nM-3 μM Spebrutinib. Cells are then incubated in the presence of compound for 1 hour at 37°C. Following incubation, cells are centrifuged and resuspended in 100 μL of serum-free RPMI and BCR is stimulated with addition of 5 μg/mL α-human IgM. Samples are centrifuged, washed in phosphate-buffered saline (PBS), and lysed in 100 μL of Cell Extraction Buffer plus 1:10 (v/v) PhosSTOP Phosphatase Inhibitor and 1:10 (v/v) Complete Protease Inhibitor. Antibodies used for immunoblot analysis include P-PLCγ2, PLCγ2 (3871; CST), Syk (2712; CST), P-Syk (2710; CST), Btk, P-Btk, and Tubulin. Membranes are scanned on a Li-Cor Odyssey scanner using infrared fluorescence detection[1].

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

CUSTOMER VALIDATION

- Blood. 2016 Jun 23;127(25):3237-52.
- Br J Pharmacol. 2019 Dec;176(23):4491-4509.
- Stem Cell Reports. 2019 May 14;12(5):996-1006.
- R Soc Open Sci. 2019 Jun 5;6(6):190434.
- Leuk Res. 2020 Jan;88:106286.

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REFERENCES

[1]. Evans EK, et al. Inhibition of Btk with CC-292 provides early pharmacodynamic assessment of activity in mice and humans. J Pharmacol Exp Ther. 2013 Aug;346(2):219-28.

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