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产品名称：SHP099 hydrochloride
产品别名：SHP099 hydrochloride

生物活性：

Description	SHP099 hydrochloride is a potent, selective and orally available SHP2 inhibitor with an IC_{50} of 70 nM.
IC_{50} & Target	IC50: 70 nM (SHP2)[1]
In Vitro	The X-ray co-crystal for SHP099 with SHP2 reveals a new interaction with the basic amine and the Phe113 backbone carbonyl. SHP099 shows inhibition of cell proliferation (KYSE-520 model) with an IC_{50} of 1.4 μM. SHP099 shows high solubility and high permeability with no apparent efflux in Caco-2 cells[1]. SHP099 concurrently binds to the interface of the N-terminal SH2, C-terminal SH2, and protein tyrosine phosphatase domains, thus inhibiting SHP2 activity through an allosteric mechanism. SHP099 suppresses RAS–ERK signalling to inhibit the proliferation of receptor-tyrosine-kinase-driven human cancer cells[2].
In Vivo	After a single doses of 30 and 100 mg/kg (red and blue lines, respectively), dose-dependent exposure and modulation of the pharmacodynamic marker p-ERK is observed in the xenografts. A daily oral dose of 10 or 30 mg/kg yield 19% and 61% tumor growth inhibition, respectively. Tumor stasis is achieved at 100 mg/kg[1].
Solvent&Solubility	***In Vitro:*** **Methanol : 15 mg/mL** (**38.59 mM;** Need ultrasonic) **DMSO : 4.1 mg/mL** (**10.55 mM;** Need ultrasonic and warming) **H_2O : ≥ 2.5 mg/mL** (**6.43 mM**) * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5725 mL	12.8627 mL	25.7255 mL
	5 mM	0.5145 mL	2.5725 mL	5.1451 mL
	10 mM	0.2573 mL	1.2863 mL	2.5725 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

1.SHP099 hydrochloride is resuspended in 0.6% methylcellulose, 0.5% Tween80 in 0.9% saline[3].

References

[1]. Garcia Fortanet J, et al. Allosteric Inhibition of SHP2: Identification of a Potent, Selective, and Orally Efficacious Phosphatase Inhibitor. J Med Chem. 2016 Sep 8;59(17):7773-82.

[2]. Chen YN, et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. Nature. 2016 Jul 7;535(7610):148-52.

[3]. Carmine Fedele, et al. SHP2 Inhibition Abrogates MEK inhibitor Resistance in Multiple Cancer Models. bioRxiv. April 25, 2018.

实验参考：

Cells are plated onto 96-well plates in 100 μL medium. SHP099 with various concentrations (1.25, 2.5, 5,

Cell Assay	10, 20 μM) are added 24 h after cell plating. At day 5, 50 μL Celltiter-Glo reagent is added, and the luminescent signal is determined[1].
Kinase Assay	The inhibition of SHP2 from the tested compounds (SHP099) concentrations varying from 0.003-100 μM is monitored using an assay in which 0.5 nM of SHP2 is incubated with of 0.5 μM of peptide IRS1_pY1172(dPEG8)pY1222. After 30-60 minutes incubation at the surrogate substrate, DiFMUP is added to the reaction and incubated at 25 °C for 30 minutes. The reaction is then quenched by the addition of 5 μL of a 160 μM solution of bpV(Phen). The fluorescence signal is monitored using a microplate reader using excitation and emission wavelengths of 340 nm and 450 nm, respectively[1].
References	[1]. Garcia Fortanet J, et al. Allosteric Inhibition of SHP2: Identification of a Potent, Selective, and Orally Efficacious Phosphatase Inhibitor. J Med Chem. 2016 Sep 8;59(17):7773-82. [2]. Chen YN, et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. Nature. 2016 Jul 7;535(7610):148-52. [3]. Carmine Fedele, et al. SHP2 Inhibition Abrogates MEK inhibitor Resistance in Multiple Cancer Models. bioRxiv. April 25, 2018.