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产品名称：REGORAFENIB 盐酸盐
产品别名：Regorafenib Hydrochloride；瑞戈非尼盐酸盐；BAY73-4506 hydrochloride

生物活性：

Description

Regorafenib Hydrochloride is a multi-target inhibitor for VEGFR1/2/3, PDGFRβ, Kit, RET and Raf-1 with IC50s of 13/4.2/46, 22, 7, 1.5 and 2.5 nM, respectively.

IC_{50} & Target

VEGFR1	VEGFR2	VEGFR3	PDGFRβ	Braf	$BRaf^{V600E}$
13 nM (IC_{50})	4.2 nM (IC_{50})	46 nM (IC_{50})	22 nM (IC_{50})	28 nM (IC_{50})	19 nM (IC_{50})

Raf-1

2.5 nM (IC_{50})

In Vitro

Regorafenib potently inhibits VEGFR2 autophosphorylation in NIH-3T3/VEGFR2 cells with an IC50 of 3 nM. In HAoSMCs, regorafenib inhibits PDGFR-β autophosphorylation after stimulation with PDGF-BB, with an IC50 of 90 nM. Regorafenib inhibits the proliferation of VEGF165-stimulated HUVECs, with an IC50 of 3 nM[1]. Regorafenib causes a concentration-dependent decrease in Hep3B cell growth, having an IC50 of 5 μM. Regorafenib subsequently increases the levels of phospho-c-Jun, a JNK target, but not total c-Jun in Hep3B cells[3].

In Vivo

Regorafenib effectively inhibits growth of the Colo-205 xenografts in the dose range of 10-100 mg/kg reaching a TGI of 75% at day 14 at the 10 mg/kg dose. In the MDA-MB-231 model, regorafenib is highly efficacious at a dose as low as 3 mg/kg, resulting in a significant TGI of 81%, which increases to 93% at doses of 10 and 30 mg/kg, where tumor stasis is reached[1].

Solvent&Solubility

In Vitro:

DMSO : ≥ 5.6 mg/mL (10.78 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9257 mL	9.6287 mL	19.2574 mL
	5 mM	0.3851 mL	1.9257 mL	3.8515 mL
	10 mM	0.1926 mL	0.9629 mL	1.9257 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。

References

[1]. Wilhelm SM, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer, 2011, 129(1), 245-255.

[2]. Heng DY, et al. Targeted therapy for metastatic renal cell carcinoma: current treatment and future directions. Ther Adv Med Oncol, 2010, 2(1), 39-49.

[3]. Carr BI, et al. Fluoro-Sorafenib (Regorafenib) effects on hepatoma cells: growth inhibition, quiescence, and recovery. J Cell Physiol, 2013, 228(2), 292-297.

实验参考：	
Cell Assay	For proliferation assays, GIST 882 and TT cells are grown in RPMI medium containing L-glutamine, and MDA-MB-231, HepG2 and A375 cells in DMEM always containing 10% hiFBS. Cells are trypsinized, plated at 5×10^4 cells/well in 96-well plates in complete media containing 10% FBS and grown overnight at 37°C. The next day, vehicle or regorafenib serially diluted in complete growth media to between 10 μM and 5 nM final concentrations, and 0.2% DMSO, is added and incubation is continued for 96 hr. Cell proliferation is quantified using CellTitre-Glo™. [1]
Animal Administration	Female athymic NCr nu/nu mice, kept in accordance with Federal guidelines, are subcutaneously inoculated with 5×10^6 Colo-205 or MDA-MB-231 cells or implanted with 1 mm^3 786-O tumor fragments. When tumors reach a volume of 100 mm^3, regorafenib or vehicle control is administered orally qd×21 in the 786-O model, and qd×9 in the Colo-205 and MDA-MB-231 models, respectively, at doses of 100, 30, 10, and 3 mg/kg. Paclitaxel is administered intravenously at 10 mg/kg in ethanol/Cremophor EL®/saline (12.5%/12.5%/75%) every 2 days×5. Tumor size (volume) is estimated twice weekly $(l\times w^2)/2$, and the percentage of tumor growth inhibition (TGI) is obtained from terminal tumor weights (1-T/C×100). Mice are weighed every other day starting from the first day of treatment. The general health status of the mice is monitored daily. [1]
Kinase Assay	Initial *in vitro* kinase inhibition profiling is performed at Millipore Corporation at a fixed 1 μM compound concentration under Millipore standard conditions [10 μM adenosine-5′-triphosphate (ATP) concentration]. Inhibitory concentration of 50% (IC_{50}) values are determined from selected responding kinases,e.g., VEGFR1 and RET. TIE2 kinase inhibition is measured with a homogeneous time-resolved fluorescence (HTRF) assay using a recombinant fusion protein of glutathione-S-transferase, the intracellular domain of TIE2 and the peptide biotin-Ahx-EPKDDAYPLYSDFG as substrate. [1]
References	[1]. Wilhelm SM, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer, 2011, 129(1), 245-255. [2]. Heng DY, et al. Targeted therapy for metastatic renal cell carcinoma: current treatment and future directions. Ther Adv Med Oncol, 2010, 2(1), 39-49. [3]. Carr BI, et al. Fluoro-Sorafenib (Regorafenib) effects on hepatoma cells: growth inhibition, quiescence, and recovery. J Cell Physiol, 2013, 228(2), 292-297.