Regorafenib

Cat. No.: HY-10331

CAS No.: 755037-03-7

Molecular Formula: $C_{21}H_{15}ClF_4N_4O_3$

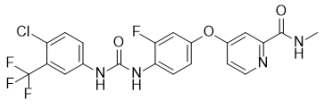
Molecular Weight: 482.82

Target: VEGFR; Autophagy; PDGFR; Raf; RET

Pathway: Protein Tyrosine Kinase/RTK; Autophagy; MAPK/ERK Pathway

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 : ≥ 260 mg/mL (538.50 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
1 mM	2.0712 mL	10.3558 mL	20.7117 mL
5 mM	0.4142 mL	2.0712 mL	4.1423 mL
10 mM	0.2071 mL	1.0356 mL	2.0712 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 (5.18 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.18 mM); Suspended solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.18 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Regorafenib (BAY 73-4506) is a multi-targeted receptor tyrosine kinase inhibitor with IC_{50}s of 13/4.2/46, 22, 7, 1.5 and 2.5 nM for VEGFR1/2/3, PDGFRβ, Kit, RET and Raf-1, respectively.

IC_{50} & Target

VEGFR1	VEGFR2	VEGFR3	PDGFRβ
13 nM (IC_{50})	4.2 nM (IC_{50})	46 nM (IC_{50})	22 nM (IC_{50})

	Raf-1 2.5 nM (IC_{50})	Braf 28 nM (IC_{50})	$BRaf^{V600E}$ 19 nM (IC_{50})
In Vitro	Regorafenib potently inhibits VEGFR2 autophosphorylation in NIH-3T3/VEGFR2 cells with an IC_{50} of 3 nM. In HAoSMCs, regorafenib inhibits PDGFR-β autophosphorylation after stimulation with PDGF-BB, with an IC_{50} of 90 nM. Regorafenib inhibits the proliferation of VEGF165-stimulated HUVECs, with an IC_{50} of 3 nM[1]. Regorafenib causes a concentration-dependent decrease in Hep3B cell growth, having an IC_{50} of 5 μM. Regorafenib subsequently increases the levels of phospho-c-Jun, a JNK target, but not total c-Jun in Hep3B cells[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.		
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.		

PROTOCOL

Cell Assay [1]	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™. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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. NSC 125973 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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Discov. 2019 Dec;9(12):1686-1695.
- Cell Res. 2020 Sep;30(9):779-793.
- Sci Transl Med. 2018 Jul 18;10(450). pii: eaaq1093.
- Autophagy. 2020 Jan;16(1):106-122.
- J Exp Clin Cancer Res. 2018 Jan 22;37(1):11.

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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-Bay 43-9006 (Regorafenib) effects on hepatoma cells: growth inhibition, quiescence, and recovery. J Cell Physiol, 2013, 228(2), 292-297.

[4]. Wagner J, et al. Anti-tumor effects of ONC201 in combination with VEGF-inhibitors significantly impacts colorectal cancer growth and survival in vivo through complementary non-overlapping mechanisms. J Exp Clin Cancer Res. 2018 Jan 22;37(1):11.

[5]. Matsuoka K, et al. Effective Sequential Combined Chemotherapy with Tipiracil and Regorafenib in Human Colorectal Cancer Cells. Int J Mol Sci. 2018 Sep 25;19(10). pii: E2915.

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