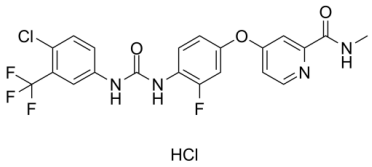
Data Sheet

Product Name:	Regorafenib (Hydrochloride)
Cat. No.:	CS-0725
CAS No.:	835621-07-3
Molecular Formula:	C21H16Cl2F4N4O3
Molecular Weight:	519.28
Target:	Autophagy; PDGFR; Raf; RET; VEGFR
Pathway:	Autophagy; MAPK/ERK Pathway; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 5.6 mg/mL (10.78 mM)



BIOLOGICAL ACTIVITY:

Regorafenib Hydrochloride is a multi-target inhibitor for **VEGFR1/2/3**, **PDGFRβ**, **Kit**, **RET** and **Raf-1** with **IC_{50}**s of 13/4.2/46, 22, 7, 1.5 and 2.5 nM, respectively. IC50 & Target: IC50: 13 nM (VEGFR1), 4.2 nM (VEGFR2), 46 nM (VEGFR3), 22 nM (PDGFRβ), 7 nM (Kit), 1.5 nM (RET), 2.5 nM (Raf-1) **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]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. **Cell Assay:** Regorafenib is diluted in complete growth media to between 10 μM and 5 nM final concentrations.[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™. **Animal Administration:** Regorafenib is formulated as a solution in either PEG400/125 mM aqueous methanesulfonic acid (80/20) or polypropylene glycol/PEG400/Pluronic F68 (42.5/42.5/15 + 20% Aqua).[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. 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.

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.

CAIndexNames:

2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-fluorophenoxy]-N-methyl-, hydrochloride (1:1)

SMILES:

ClC1=C(C(F)(F)F)C=C(NC(NC2=C(F)C=C(OC3=CC=NC(C(NC)=O)=C3)C=C2)=O)C=C1.Cl

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