Sorafenib (Nexavar) Datasheet

Technical Data

| Molecular Weight (MW) | 637.03 |
| Formula | C21H16ClF3N4O3.C2H5O2S |
| CAS No. | 475207-59-1, 284461-73-0 (free base) |
| Synonyms | Bay 43-9006 |

Solubility (25°C)

- DM2O 127 mg/mL |
- Water <1 mg/mL |
- Ethanol <1 mg/mL

Storage

- Powder 2 years -20°C |
- 2 weeks 4°C in DM2O |
- 6 months -80°C in DM2O

Biological Activity

**Description**

Sorafenib Tosylate (Bay 43-9006, Nexavar) is a multi-target inhibitor of Raf-1, B-Raf and VEGFR2 with IC50 of 6 nM, 22 nM and 90 nM, respectively.

**Targets**

- Raf-1
- B-Raf
- VEGFR2

**IC50**

- 6 nM
- 22 nM
- 90 nM

**In vitro**

Sorafenib tosylate inhibits both wild-type and V599E mutant B-Raf activity with IC50 of 22 nM and 38 nM, respectively. Sorafenib tosylate also potently inhibits mVEGFR2 (Flk-1), mVGF3, mPDGFR, Flk-1, and c-Kit with IC50 of 15 nM, 20 nM, 57 nM, 58 nM, and 68 nM, respectively. Sorafenib tosylate weakly inhibits FGFR-1 with IC50 of 580 nM. Sorafenib tosylate is not active against ERK-1, MEK-1, EGRF, HER-2, IGF1R, c-Met, PKB, PDK, pdk1, cyclinB, PKCa, PKCy, and pim-1. Sorafenib tosylate markedly inhibits VEGFR2 phosphorylation in NIH 3T3 cells with IC50 of 30 nM and Flk-3 phosphorylation in Hek-293 cells with IC50 of 20 nM. Sorafenib tosylate potently blocks MEK 1/2 and ERK 1/2 phosphorylation in most cell lines but not in A549 or H460 cells, while having no effect on inhibition of the PKB pathway. Sorafenib tosylate inhibits the proliferation of Ha58MC and MDA-MB-231 cells with IC50 of 0.28 μM and 2.6 μM, respectively. In addition to inhibition of the RAF/MEK/ERK signaling pathway, Sorafenib tosylate significantly inhibits the phosphorylation of eIF4E and down-regulates Mcl-1 levels in hepatocellular carcinoma (HCC) cells in a MEK/ERK-independent manner. Sorafenib tosylate inhibits the proliferation of PLC/PRF/S and HepG2 cells with IC50 of 6.3 μM and 4.5 μM, respectively, and leads to the significant induction of apoptosis.

**In vivo**

Onal administration of Sorafenib tosylate (~60 mg/kg) demonstrates broad spectrum, dose-dependent anti-tumor activity against a variety of human tumor xenograft models including MDA-MB-231, Colo-205, HT-29, DLD-1, NCI-H460, and A549, with no evidence of toxicity. In association with the anti-tumor efficacy, Sorafenib tosylate treatment potently inhibits MEK 1/2 phosphorylation and pERK 1/2 levels in HT-29 and MDA-MB-231 xenografts but not in Colo-205 xenografts, and significantly suppresses tumor microvessel area (MVA) and microvessel density (MVD) in MDA-MB-231, HT-29 and Colo-205 tumor xenografts. Sorafenib tosylate treatment produces dose-dependent growth inhibition of PLC/PRF/S tumor xenografts in SCID mice with TGI of 49% and 78% at 10 mg/kg and 30 mg/kg, respectively, consistent with the inhibition of ERK and eIF4E phosphorylation, reduction of the microvessel area, and induction of tumor cell apoptosis.

**Clinical Trials**

Sorafenib sensitizes bax+/- cells to TRAIL in a dose-dependent manner, through a mechanism involving down-regulating NF-κB mediated Mcl-1 and cIAP2 expression. Combining Sorafenib (30-60 mg/kg) with TRAIL (5 mg/kg) show dramatic efficacy in TRAIL-resistant HCT116 bax+/- and HT29 tumor xenografts. A Phase II study of Sorafenib combined with transarterial chemoembolization (TACE) in treating HBV-infected patients with intermediate hepatocellular carcinoma is currently ongoing.

**Features**

- Recombinant baculoviruses expressing Raf-1 (residues 305–648) and B-Raf (residues 409–765) are purified as fusion proteins. Full-length human MEK-1 is generated by PCR and purified as a fusion protein from Escherichia coli lysates. Sorafenib tosylate is added to a mixture of Raf-1 (80 ng), or B-Raf (80 ng) with MEK-1 in lysis buffer (20 mM Tris (pH 8.2), 100 mM NaCl, 5 mM MgCl2, and 0.15% β-mercaptoethanol) at a final concentration of 1% DM2O. The Raf kinase assay (final volume of 50 μL) is initiated by adding 25 μL of 10 μM [33P]ATP (400 Ci/mmol) and incubated at 32 °C for 25 minutes. Phosphorylated MEK-1 is harvested by filtration onto a microvessel area (MVA) and microvessel density (MVD) in MDA-MB-231, HT-29 and Colo-205 tumor xenografts. Sorafenib tosylate treatment produces dose-dependent growth inhibition of PLC/PRF/S tumor xenografts in SCID mice with TGI of 49% and 78% at 10 mg/kg and 30 mg/kg, respectively, consistent with the inhibition of ERK and eIF4E phosphorylation, reduction of the microvessel area, and induction of tumor cell apoptosis.

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enzyme initiation. A 50-fold stock plate is made with Sorafenib tosylate serially diluted 1:3 in a 50% DMSO/50% distilled water solution. Final Sorafenib tosylate concentrations range from 10 μM to 4.56 nM in 1% DMSO.

### Cell Assay: [1]

**Cell Lines**
MDA-MB-231, and HAsSMC

**Concentrations**
Dissolved in DMSO, final concentrations ~10 μM

**Incubation Time**
72 hours

**Methods**
Cells are exposed to increasing concentrations of Sorafenib tosylate for 72 hours. Cell number is quantitated using the Cell TiterGlo ATP Luminescent assay kit. This assay measures the number of viable cells per well by measurement of luminescent signal based on amount of cellular ATP.

### Animal Study: [1]

**Animal Models**
Female NCr-nu/nu mice implanted s.c. with MDA-MB-231, Colo-205, HT-29, H460, or A549 cells

**Formulation**
Dissolved in Cremophor EL/ethanol (50:50) as 4-fold (4×) stock solution, and diluted to 1× with water

**Doses**
~60 mg/kg

**Administration**
Orally once daily

### References


### Customer Reviews

Data from [J Invest Dermatol, 2011 September, 131:1886–1895]

Sorafenib (Nexavar) purchased from Selleck
Inhibition of the MAPK signaling pathway results in downregulation of Plk-1 protein expression. (a) WB analysis for Plk-1 protein after treatment of human melanoma cell lines M14 and WM-115 with MEK 1/2 inhibitor PD98059 (10 mM), JNK inhibitor (16 mM), p38 inhibitor SB203580 (20 mM), and multikinase inhibitor sorafenib (10 μM) for 48 h showing significant reduction in the expression of Plk-1 protein after 48 hours. (b) Annexin V/PI staining of cells treated with MAPK inhibitors and induction of apoptosis. JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK 1/2, mitogen-activated protein kinase kinase 1/2; Plk-1, polo-like kinase 1; WB, western blot.

**PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.**

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