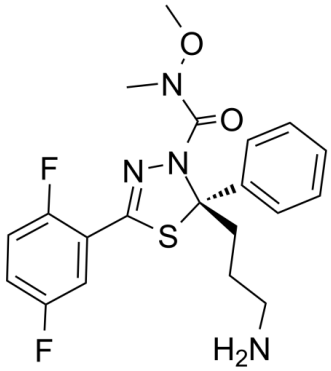
Data Sheet

Product Name:	Filanesib
Cat. No.:	CS-0867
CAS No.:	885060-09-3
Molecular Formula:	C20H22F2N4O2S
Molecular Weight:	420.48
Target:	Kinesin
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton
Solubility:	DMSO : ≥ 100 mg/mL (237.82 mM)



BIOLOGICAL ACTIVITY:

Filanesib (ARRY-520) is a synthetic **kinesin spindle protein (KSP)** inhibitor with **IC_{50}** of 6 nM. IC50 & Target: IC50: 6 nM (KSP)[1] **In Vitro:** Filanesib (ARRY-520) retains activity in multidrug-resistant cell lines. The EC_{50}s of Filanesib (ARRY-520) for inhibition of proliferation of HCT-15, NCI/ADR-RES and K562/ADR cells are 3.7, 14 and 4.2 nM respectively. Filanesib (ARRY-520) (10 nM) blocks a majority of cells in mitosis with the monopolar spindle structure typical of KSP inhibition[1]. Filanesib (ARRY-520) (10 nM) induces mitotic arrest as judged by both increased phosphorylation of histone H3 (pHH3) and accumulation of cyclin B1 in four cells[2]. Filanesib (ARRY-520) and Paclitaxel exhibit the same cytotoxic effect on Type I and II cells. The GI_{50} at 48 h for Type II EOC cells is 0.0015 μM for ARRY-520. For Type I EOC cells, the GI_{50} at 48 h is > 3 μM for ARRY-520[3]. Filanesib (ARRY-520) (1 nM) induces significant G2M cell cycle block in OCI-AML3 cells at 24 hours[4]. **In Vivo:** Filanesib (ARRY-520) (10, 15, 20, 30 mg/kg, i.p.) is active in UISO-BCA-1 xenograft, and also superior to paclitaxel in mice bearing subcutaneous HT-29, HCT-116, MDA-MB-231 and A2780 xenografts. ARRY-520 is superior to docetaxel in the androgen receptor-negative prostate cancer xenograft model PC-3, and is also superior to docetaxel in the DU145 prostate xenograft model[1]. RPMI 8226 tumor xenografts are particularly sensitive to low doses of ARRY-520 (12.5 mg/kg, i.p.)[2]. ARRY-520 significantly inhibits tumor growth in HL60 and MV4-11 xenografts of SCID mice at concentrations of 27 mg/kg and 20 mg/kg, respectively[4].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Filanesib (ARRY-520) is dissolved in DMSO.[4]Exponentially growing cells (0.4×10^6/mL) are treated with Filanesib (ARRY-520) for up to 48 hours. For combination, HL-60 and HL-60Bcl-2 cells (0.4×10^6/mL) are incubated with Filanesib (ARRY-520), ABT-737, or both for up to 96 hours. DMSO is used as the control agent. Apoptosis is estimated by flow cytometry measurements of phosphatidyl serine with the Annexin-V-FLUOS Staining Kit. Membrane integrity is simultaneously assessed by 7-amino-actinomycin D (7-AAD). To measure changes in the mitochondrial membrane potential (MMP), cells are loaded with CMXRos (300 nM) and MitoTracker Green (500 nM) for 1 hour at 37°C. The loss of MMP is then assessed by measuring CMXRos retention while simultaneously adjusting for mitochondrial mass. **Animal Administration:** Filanesib (ARRY-520) is formulated in either 25% polyethylene glycol (PEG)-400/10% EtOH/65% normal saline or 100% normal saline.[1]Subcutaneous tumor xenografts are allowed to grow to a volume of 250-350 mm^3. The mice are randomized into groups of 3-4 based on tumor size, and are given a single dose of Filanesib (ARRY-520) i.p. At various time-points after administration of the drug, the mice are euthanized by CO_2 inhalation and the tumors excised and placed in 10% neutral buffered formalin. The formalin-fixed tumors are processed and paraffin embedded by standard procedures. Spindle morphology is analyzed by staining tumor sections for α-tubulin, and apoptosis is analyzed by TUNEL stain. Monopolar/abnormal spindles and TUNEL positive (apoptotic) cells are counted in three ×40 fields from each sample, analyzed using algorithms developed in ImagePro software.

References:

[1]. Woessner R, et al. ARRY-520, a novel KSP inhibitor with potent activity in hematological and taxane-resistant tumor models. Anticancer Res. 2009 Nov;29(11):4373-80.

[2]. Tunquist BJ, et al. Mcl-1 stability determines mitotic cell fate of human multiple myeloma tumor cells treated with the kinesin spindle protein inhibitor ARRY-520. Mol Cancer Ther. 2010 Jul;9(7):2046-56.

[3]. Kim KH, et al. KSP inhibitor ARRY-520 as a substitute for Paclitaxel in Type I ovarian cancer cells. J Transl Med. 2009 Jul 20;7:63.

[4]. Carter BZ, et al. Inhibition of KSP by ARRY-520 induces cell cycle block and cell death via the mitochondrial pathway in AML cells. Leukemia. 2009 Oct;23(10):1755-62.

CAIndexNames:

1,3,4-Thiadiazole-3(2H)-carboxamide, 2-(3-aminopropyl)-5-(2,5-difluorophenyl)-N-methoxy-N-methyl-2-phenyl-, (2S)-

SMILES:

O=C(N1[C@@](C2=CC=CC=C2)(CCCN)SC(C3=CC(F)=CC=C3F)=N1)N(OC)C

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