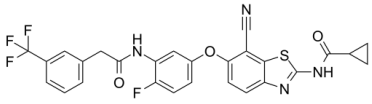
Data Sheet

Product Name:	TAK-632
Cat. No.:	CS-1697
CAS No.:	1228591-30-7
Molecular Formula:	C27H18F4N4O3S
Molecular Weight:	554.52
Target:	Aurora Kinase; Raf
Pathway:	Cell Cycle/DNA Damage; Epigenetics; MAPK/ERK Pathway
Solubility:	DMSO : 100 mg/mL (180.34 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

TAK-632 is a potent **pan-RAF** inhibitor with **IC_{50}** of 1.4, 2.4 and 8.3 nM for **CRAF**, **$BRAF^{V600E}$**, **$BRAF^{WT}$**, respectively. IC50 & Target: IC50: 1.4 nM (C-RAF), 2.4 nM ($BRAF^{V600E}$), 8.3 nM ($BRAF^{WT}$),66 nM (Aurora B), 160 nM (VEGFR)[1] **In Vitro:** TAK-632 inhibits PDGFRβ, FGFR3, GSK3β, CDK2, P38α, PDGFRα, TIE2, and CDK1 with a range of IC_{50} values from 120-790 nM. CHK1, IKKβ, and MEK1 are inhibited over an IC_{50} range of 1400-1700 nM. With 1 h of preincubation time, TAK-632 inhibits BRAF and CRAF in an ATP competitive manner (at low ATP concentrations BRAF IC_{50}: 15 nM; CRAF: 8.1 nM). The respective biochemical activity of TAK-632 against BRAF and CRAF reduces to IC_{50} values of 58 nM and 62 nM at high ATP concentrations.TAK-632 demonstrates strong inhibition of pMEK and pERK in HMVII cells with IC_{50} values of 49 nM and 50 nM, respectively[1]. TAK-632 shows strong antiproliferative effects both in A375 and SK-MEL-2 cells (GI_{50} of 40-190 nM in A375 cells and GI_{50} of 190-250 nM in SK-MEL-2 cells)[2]. **In Vivo:** TAK-632 demonstrates dramatically improved solubility (740 μg/mL) in pH 6.8 phosphate buffer and exhibits significant oral absorption (at a dose of 25 mg/kg, AUC, 32.47 μg h/mL; F, 51.7%) in rats. In a dog PK study, 10 mg/kg administration of TAK-632 also shows superior oral bioavailability (F: 108%).Oral single administration of TAK-632 inhibits pERK in tumors at 8 h after its administration over a dose range of 1.9-24.1 mg/kg. In particular, 9.7-24.1 mg/kg dosing with TAK-632 strongly inhibits pERK levels to 11% of the control. TAK-632 exhibits dose-dependent antitumor efficacy without severe body weight reduction over a dose range of 3.9-24.1 mg/kg. Significant tumor regression is observed at 9.7 mg/kg and 24.1 mg/kg (T/C=−2.1% and −12.1%, respectively)[1]. TAK-632 exhibits potent antitumor efficacy when orally administered at 60 mg/kg once daily (T/C=37%, P<0.001) or at 120 mg/kg once daily (T/C=29%, P<0.001) for 21 days without severe toxicity in NRAS-mutant melanoma using a SK-MEL-2 xenograft model[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [2]Immunoprecipitated BRAF or CRAF is incubated with recombinant inactive MEK (K97R) at 30°C for 30 minutes in kinase reaction buffer containing ATP/Mg^{2+}. RAS/RAF wild-type (A431, CsFb, and HeLa), KRAS-mutant (A549, HCT-116, and MIA PaCa-2), and NRAS-mutant melanoma (GAK, HMV-II, and SK-MEL-2) cells are treated with TAK-632 (0, 0.32, 1.6, 8, 40, 200, 1000 and 5000 nM) at the indicated concentrations for 2 hours. Cell lysates are analyzed by Western blot analysis[2]. **Cell Assay:** TAK-632 is dissolved in DMSO and stored, and then diluted with appropriate media before use[2]. [2]Cell viability is assessed (3 replicates) using the Sulforhodamine B assay or by the CellTiter-Glo luminescent cell viability assay. The concentrations of TAK-632 that produced 50% growth inhibition (GI_{50}) are calculated using PCP software. The combination index (CI) is calculated using CalcuSyn software. To investigate the antiproliferative activity of TAK-632, we performed proliferation assays in various cell lines harboring mutated BRAF, NRAS, or KRAS. HMV-II, SK-MEL-2, or A375 cells are cotreated with TAK-632 and TAK-733 at the indicated concentrations for 72 hours. Cell viability is measured. The CI value at EC_{50} is calculated. A375 cells stably expressing $NRAS^{Q61K}$ or ΔN-BRAF are cotreated with TAK-632 and TAK-733 at the indicated concentrations for 72 hours. Cell viability is measured. The CI value at EC_{50} is calculated[2]. **Animal Administration:** TAK-632 is formulated as a suspension in distilled water (Mice)[2].[2]Mice[2]
The xenograft-implanted nude mice are used. Mice bearing SK-MEL-2 xenografts are treated once daily for 21 consecutive days with

vehicle or TAK-632 at the indicated concentrations (10 mice per each treatment group). Day 0 indicates the beginning of treatment. Tumors are measured twice a week. Mice bearing SK-MEL-2 xenografts are treated once daily (QD) for 3 days with vehicle, TAK-632 at 60 mg/kg (60 mpk), or TAK-632 at 120 mg/kg (120 mpk). Tumor xenografts are obtained at indicated time points after the final treatment and analyzed by Western blot analysis. Individual blots with dividing lines are combined from a single electrophoresis gel. Bars represent densitometric analysis of phospho-ERK, normalized to vehicle-treated control (mean±SD).

References:

[1]. Okaniwa M, et al. Discovery of a selective kinase inhibitor (TAK-632) targeting pan-RAF inhibition: design, synthesis, and biological evaluation of C-7-substituted 1,3-benzothiazole derivatives. J Med Chem. 2013 Aug 22;56(16):6478-94.

[2]. Nakamura A, et al. Antitumor activity of the selective pan-RAF inhibitor TAK-632 in BRAF inhibitor-resistant melanoma. Cancer Res. 2013 Oct 11.

CAIndexNames:

Benzeneacetamide, N-[5-[[7-cyano-2-[(cyclopropylcarbonyl)amino]-6-benzothiazolyl]oxy]-2-fluorophenyl]-3-(trifluoromethyl)-

SMILES:

O=C(NC1=CC(OC2=CC=C3N=C(NC(C4CC4)=O)SC3=C2C#N)=CC=C1F)CC5=CC=CC(C(F)(F)F)=C5

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