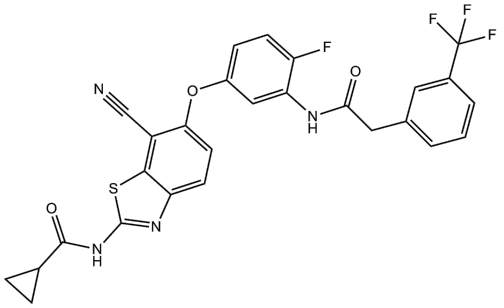
Product Data Sheet

Product Name: TAK-632
Cat. No.: GC17455

Chemical Properties

Cas. No.	1228591-30-7		
Chemical Name	N-[7-cyano-6-[4-fluoro-3-[[2-[3-(trifluoromethyl)phenyl]acetyl]amino]phenoxy]-1,3-benzothiazol-2-yl]cyclopropanecarboxamide		
SMILES	C1CC1C(=O)NC2=NC3=C(S2)C(=C(C=C3)OC4=CC(=C(C=C4)F)NC(=O)CC5=CC(=CC=C5)C(F)(F)F)C#N		
Formula	$C_{27}H_{18}F_4N_4O_3S$	M.Wt	554.52
Solubility	≥ 27.75mg/mL in DMSO, ≥ 2.23 mg/mL in EtOH with ultrasonic and warming	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure			

Protocol

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Kinase experiment: Immunoprecipitated BRAF or CRAF is incubated with recombinant inactive MEK (K97R) at 30°C for 30 minutes in kinase reaction buffer containing ATP/Mg2+. 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 experiment: 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 (GI50) 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 EC50 is calculated. A375 cells stably expressing NRASQ61K 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 EC50 is calculated[2].

Animal experiment: 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).

Caution: Product has not been fully validated for medical applications. For research use only.
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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.

Background

TAK-632 is a selective inhibitor of BRAF, CRAF and BRAF-V600E kinase with IC50 value of 8.3 nM, 1.4 nM and 2.4 nM [1].

RAF kinases are a family of three serine/threonine-specific protein kinases and play an important role in the RAS-RAF-MEK-ERK signal transduction cascade, as well as the mitogen-activated protein kinase (MAPK) cascade [2].

TAK-632 is a potent pan-RAF kinase inhibitor and has a higher selectivity compared with the reported pan-RAF kinase inhibitor vemurafenib. When tested with SK-MEL-2 cells, TAK-632 showed induction on the BRAF-CRAF dimmers formation in a dose-dependent manner. In melanoma cell lines A375 and SK-MEL-2, TAK-632 exhibited significant antiproliferative effects with GI50 value of 6 nom/L and 11 nom/L, respectively [1].

In mouse model with SK-MEL-2 subcutaneous xenograft, oral administration of TAK-632 caused significant reduction of phosphorylated ERK and tumor growth at the dose of 60 or 120 mg/kg/d once daily for 21 days without severe toxicity [1].

It is also reported that TAK-632 is a potent inhibitor of pERK with IC50 value of 25 nM [1].

References:
[1]. Nakamura, A., et al., Antitumor activity of the selective pan-RAF inhibitor TAK-632 in BRAF inhibitor-resistant melanoma. Cancer Res, 2013. 73(23): p. 7043-55.
[2]. Korkut, A., et al., Perturbation biology nominates upstream-downstream drug combinations in RAF inhibitor resistant melanoma cells. Elife, 2015. 4.