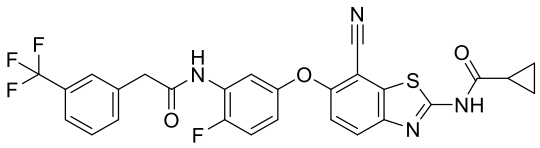
Product data sheet

MedKoo Cat#: 406295 Name: TAK-632 CAS#: 1228591-30-7 Chemical Formula: $C_{27}H_{18}F_4N_4O_3S$ Exact Mass: 554.10357 Molecular Weight: 554.51	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
TAK-632 is a potent pan-RAF inhibitor with favorable in vitro activity (BRAF(V600E) IC50, 2.4 nM; BRAF(wt), 8.3 nM; CRAF, 1.4 nM; pMEK (A375) IC50, 12 nM; pMEK (HMVII), 49 nM; V/B ratio. In addition, TAK-632 was shown preclinically to be a selective kinase inhibitor targeting pan-RAF kinase activity by testing against a panel of kinases. In both A375 (BRAFV600E) and HMVII (NRASQ61K) xenograft models in rats, TAK-632 demonstrated regressive antitumor efficacy by twice daily, 14-day repetitive administration without significant body weight loss.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	30.0	54.1
Ethanol	2.0	3.6

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	1.80 mL	9.02 mL	18.03 mL
5 mM	0.36 mL	1.80 mL	3.61 mL
10 mM	0.18 mL	0.90 mL	1.80 mL
50 mM	0.04 mL	0.18 mL	0.36 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Okaniwa M, Hirose M, Arita T, Yabuki M, Nakamura A, Takagi T, Kawamoto T, Uchiyama N, Sumita A, Tsutsumi S, Tottori T, Inui Y, Sang BC, Yano J, Aertgeerts K, Yoshida S, Ishikawa T. 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. doi: 10.1021/jm400778d. Epub 2013 Aug 1. PMID: 23906342.

2. Nakamura A, Arita T, Tsuchiya S, Donelan J, Chouitar J, Carideo E, Galvin K, Okaniwa M, Ishikawa T, Yoshida S. Antitumor activity of the selective pan-RAF inhibitor TAK-632 in BRAF inhibitor-resistant melanoma. Cancer Res. 2013 Dec 1;73(23):7043-55. doi: 10.1158/0008-5472.CAN-13-1825. Epub 2013 Oct 11. PMID: 24121489.

In vivo study

1. Okaniwa M, Hirose M, Arita T, Yabuki M, Nakamura A, Takagi T, Kawamoto T, Uchiyama N, Sumita A, Tsutsumi S, Tottori T, Inui Y, Sang BC, Yano J, Aertgeerts K, Yoshida S, Ishikawa T. Discovery of a selective kinase inhibitor (TAK-632) targeting pan-

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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. doi: 10.1021/jm400778d. Epub 2013 Aug 1. PMID: 23906342.

7. Bioactivity

Biological target:

TAK-632 is a potent pan-RAF inhibitor with IC50 of 1.4, 2.4 and 8.3 nM for CRAF, BRAFV600E, BRAFWT, respectively.

In vitro activity

The selective pan-RAF inhibitor TAK-632 suppresses RAF activity in BRAF wild-type cells with minimal RAF paradoxical activation. Using RNAi and TAK-632 in preclinical models reveals that the MAPK pathway of NRAS-mutated melanoma cells is highly dependent on RAF. TAK-632 induces RAF dimerization but inhibits the kinase activity of the RAF dimer, probably because of its slow dissociation from RAF. As a result, TAK-632 demonstrates potent antiproliferative effects both on NRAS-mutated melanoma cells and BRAF-mutated melanoma cells with acquired resistance to BRAF inhibitors through NRAS mutation or BRAF truncation. Furthermore, the combination of TAK-632 and the MAPK kinase (MEK) inhibitor TAK-733 exhibits synergistic antiproliferative effects on these cells. The unique features of TAK-632 as a pan-RAF inhibitor provide rationale for its further investigation in NRAS-mutated melanoma and a subset of BRAF-mutated melanomas refractory to BRAF inhibitors.

Reference: Cancer Res. 2013 Dec 1;73(23):7043-55. http://cancerres.aacrjournals.org/cgi/pmidlookup?view=long&pmid=24121489

In vivo activity

In vivo efficacy of TAK-632 (8B) was evaluated using an SD formulation in a human melanoma A375 (BRAFV600E) xenograft model in F344 nude rats. Reflecting the potent in vitro pMEK inhibition, oral single administration of 8B inhibited pERK in tumors at 8 h after its administration over a dose range of 1.9–24.1 mg/kg (Figure 7). In particular, 9.7–24.1 mg/kg dosing with 8B strongly inhibited pERK levels to 11% of the control. The antitumor efficacy of 8B was examined by administration twice daily for 14 days in an A375 xenograft model in rats (Figure 8). Compound 8B exhibited dose-dependent antitumor efficacy without severe body weight reduction over a dose range of 3.9–24.1 mg/kg. Significant tumor regression was observed at 9.7 mg/kg and 24.1 mg/kg (T/C = −2.1% and −12.1%, respectively). Next, antitumor effects of 8B in a human melanoma HMVII (NRASQ61K/BRAFG469V) xenograft model were evaluated in rats (Figure 9). In this study, 8B was orally administered as an SD formulation and suppressed the growth of HMVII tumors with T/C values of 52%, 26%, and 0% at doses of 3.9 mg/kg, 9.7 mg/kg, and 24.1 mg/kg, respectively. This antitumor efficacy was dose-dependent and significant ($p < 0.025$) compared with that of the vehicle control at all three doses. In this model, the HMVII tumor induced cancer cachexia and resulted in approximately 6% body weight loss in the vehicle control group over the 14-day administration period (body weight change: −8.6 g for the vehicle and +16.5 g for nontumor bearing). Interestingly, dose-dependent recovery of body weight loss was observed. In particular, the group at 24.1 mg/kg showed no signs of body weight loss (body weight change: +28.4 g).

Reference: J Med Chem. 2013 Aug 22;56(16):6478-94. https://doi.org/10.1021/jm400778d