ACBI3: A Chemical Probe degrader for pan KRAS

Version 1.0 (23rd June 2025)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/ACBI3

Overview

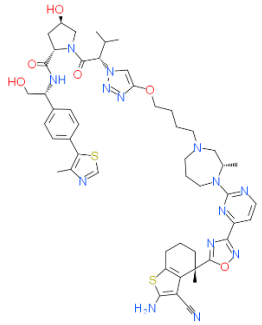
KRAS (Kirsten rat sarcoma viral oncogene homologue) is the most commonly mutated oncogene in human cancers. Variants, predominantly mutations at glycine (G) 12 or glutamine (Q) 61, increase the proportion of activated, GTP-loaded KRAS, enhancing RAF-MEK-ERK (MAPK) signalling, and drive tumour growth.

Summary

Chemical Probe Name	ACBI3 (degrader)
Negative control compound	cis-ACBI3
Target(s) (synonyms)	pan KRAS
Recommended *in vitro* assay concentration	Use at concentration between 1 -10 µM for ACBI3 and cis-ACBI3; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested with 30 mg/kg s.c. q.d .in mice; results in KRAS degradation. GP2d KRAS G12D and RKN KRAS G12V mutant tumours shrink upon ACBI3 treatment without significant body weight change.
Publications	PMID: 39298590 (Cmp. 7)
In vitro assay(s) used to characterise	SPR, FP
Cellular assay(s) for target-engagement	Degradation , proliferation assay

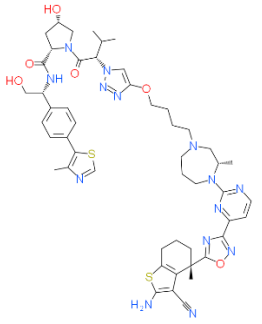
Chemical Probe & Negative Control Structures and Use

ACBI3 Chemical Probe



SMILES:
CC(C)[C@@H](C(N1C[C@@H](C[C@H]1C(N[C@@H](CO)c1ccc(cc1)c1c(C)ncs1)=O)O)=O)n1cc(nn1)OCCCCN1CCCN(c2nccc(c3nc([C@@]4(C)CCCc5c4c(C#N)c(N)s5)on3)n2)[C@@H](C)C1
InChiKey: DQRZNYPHOWVXPQ-YDUPODKQSA-N
Molecular weight: 1018.44 g/mol
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

cis-ACBI3 Negative Control



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Chemical Probe Profile

In vitro Potency & Selectivity:

Binding of ACBI3 to KRAS was demonstrated in the surface plasmon resonance assay with KRASG12D GDP (KD = 5 ± 1 nM; n = 3) and KRASG12V GDP (KD = 4 ± 1 nM; n = 3) and in the fluorescence polarization assay with VCB+KRASG12D (KD = 4 ± 1 nM; n = 3). Whole cell proteomics MS analysis of GP2d cells shows selective degradation of KRAS.

Potency in Cells and Cellular Target Engagement:

Cellular degradation was demonstrated by using capillary electrophoresis for KRASG12D (24 h, GP5d cells; DC_{50} = 2 nM) and KRASG12V (24 h, SW620 cells; DC_{50} = 7 nM) and cellular proliferation (CellTiterGlo assay, 5 days): GP5d cells (IC_{50} = 5 nM), SW620 cells (IC_{50} = 15 nM).