SGK3-PROTAC1: A Chemical Probe for SGK3

Version 1.0 (11th January 2024)

Web link: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/SGK3-PROTAC1

Overview

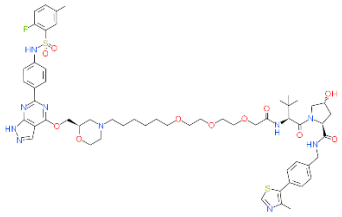
SGK3 is a phox homology (PX) domain containing protein kinase activated at endosomes downstream of class 1 and 3 PI3K family members by growth factors and oncogenic mutations. SGK3 plays a key role in mediating resistance of breast cancer cells to class 1 PI3K or Akt inhibitors, by substituting for the loss of Akt activity and restoring proliferative pathways such as mTORC1 signalling.

Summary

Chemical Probe Name	SGK3-PROTAC1 (PROTAC SGK3 degrader-1, DAT8, SGK3 degrader-1)
Negative control compound	cisSGK3-PROTAC1
Target(s) (synonyms)	SGK3 (Serum/Glucocorticoid Regulated Kinase Family Member 3)
Recommended *in vitro* assay concentration	Use at concentration of 300 nM (up to 3 µM) for SGK3-PROTAC1 and cisSGK3-PROTAC1; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Not tested.
Publications	PMID: 31461270 (DAT8)
In vitro assay(s) used to characterise	radioactive filter binding assay using ^{33P}ATP
Cellular assay(s) for target-engagement	Degradation assay

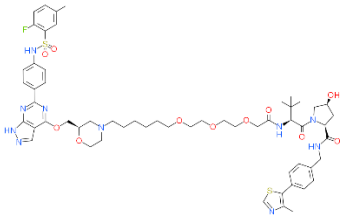
Chemical Probe & Negative Control Structures and Use

SGK3-PROTAC1 Chemical Probe



SMILES:
Cc1ccc(c(c1)S(Nc1ccc(cc1)c1nc(c2cn[nH]c2n1)OC[C@H]1CN(CCCCCCOCCOCCOCC(N[C@H](C(N2C[C@@H](C[C@H]2C(NCc2ccc(cc2)c2c(C)ncs2)=O)O)=O)C(C)(C)C)=O)CCO1)(=O)=O)F
InChiKey: RTFQFPZKDYMMMJ-RIAKQDHQSA-N
Molecular weight: 1156.49 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

cisSGK3-PROTAC1 Negative Control



SMILES:
Cc1ccc(c(c1)S(Nc1ccc(cc1)c1nc(c2cn[nH]c2n1)OC[C@H]1CN(CCCCCCOCCOCCOCC(N[C@H](C(N2C[C@H](C[C@H]2C(NCc2ccc(cc2)c2c(C)ncs2)=O)O)=O)C(C)(C)C)=O)CCO1)(=O)=O)F
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Chemical Probe Profile

In vitro Potency & Selectivity:

In the SGK3 binding assay an IC_{50} = 300 nM was measured. Closest off-targets in the Dundee Kinase panel (140 targets) at 1 µM are [% activity remaining] SGK1 (34), RPS6KB1 (S6K1) (19) with the following values in another assay [IC_{50}]: RPS6KB1 (1.8 µM), SGK1 (220 nM). The proteomic analysis of HEK293 cells is clean.

Potency in Cells and Cellular Target Engagement:

SGK3-PROTAC1 is a good SGK3 degrader: SGK3 levels were reduced by 65% without effecting SGK1, SGK2, or RPS6KB1 at 0.1 µM (HEK293 cells, 48 h). SGK3-PROTAC1 (>0.1 µM) induced degradation of SGK3, but not SGK1 or RPS6KB1 in two SGK3 dependent breast cancer cell lines, CAMA-1 and ZR-75-1.