VZ185: A Chemical Probe for BRD7 and BRD9

Version 1.0 (10th January 2024)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/VZ185

Overview

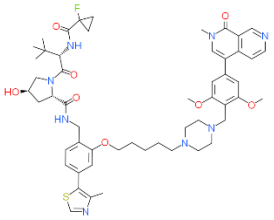
BRD9 and its close homolog BRD7 (85% sequence identity) are bromodomain-containing subunits of the BAF (BRG-/BRM-associated factor) and PBAF (polybromo associated BAF) complexes, respectively. BAF and PBAF represent two variants of the SWI/SNF complex, one of the four mammalian ATP-dependent chromatin remodeling complexes. BRD9 is overexpressed in several malignancies, such as cervical cancer and in non-small cell lung cancer (NSCLC). BRD7 gene has been proposed as candidate tumor suppressor gene. It has been recently shown that inactivation of the BRD7 gene sensitizes tumor cells to T cell-mediated killing, suggesting that knockdown of BRD7 could be an attractive target for immunotherapy.

Summary

Chemical Probe Name	VZ185 (PROTAC, degrader)
Negative control compound	cisVZ185
Target(s) (synonyms)	BRD7 and BRD9
Recommended *in vitro* assay concentration	Use at concentration of 300 nM for VZ185 and cisVZ185; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Not tested.
Publications	PMID: 30540463 (Compound 51)
In vitro assay(s) used to characterise	Isothermal titration calorimetry (ITC)
Cellular assay(s) for target-engagement	Degradation of BRD7/9 in RI-1 cells; Live cell degradation HiBiT-BRD7 and HiBiT-BRD9; Cell viability assay (CellTiterGlo)

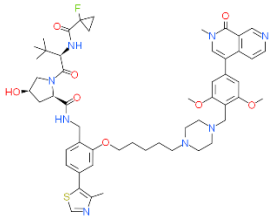
Chemical Probe & Negative Control Structures and Use

VZ185 Chemical Probe



SMILES:
Cc1c(c2ccc(CNC([C@@H]3C[C@H](CN3C([C@H](C(C)(C)C)NC(C3(CC3)F)=O)=O)O)=O)c(c2)OCCCCCN2CCN(CC2)Cc2c(cc(cc2OC)C2=CN(C)C(c3cnccc23)=O)OC)scn1
InChiKey: ZAGCLFXBHOXXEN-JPTLTNPLSA-N
Molecular weight: 994.48 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

cisVZ185 Negative Control



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Chemical Probe Profile

In vitro Potency & Selectivity:

VZ185 is a potent BRD7/9 degrader with K_D = 5.1 ± 0.6 nM for VZ185:BRD9-BD (ITC). It is highly selective with no off-targets detected in the cellular proteasome.

Potency in Cells and Cellular Target Engagement:

DC_{50} = 4.5 nM for BRD7 and 1.76 nM for BRD9 in a degradation assay in RI-1 cells after 8 h. For the live cell degradation of HiBiT-BRD7 DC_{50} = 34.5 nM and 4.0 nM for HiBiT-BRD9. VZ185 is cytotoxic in cancer cell lines with EC_{50} = 3.4 nM in EOL-1 cells and 39.8 nM in A-402 cells in the CellTiterGlo cell viability assay.