Homer: A chemical degrader probe for WDR5

Version 1.0 (28th June 2021)

Web link for more details: https://www.thesgc.org/chemical-probes/Homer

Overview

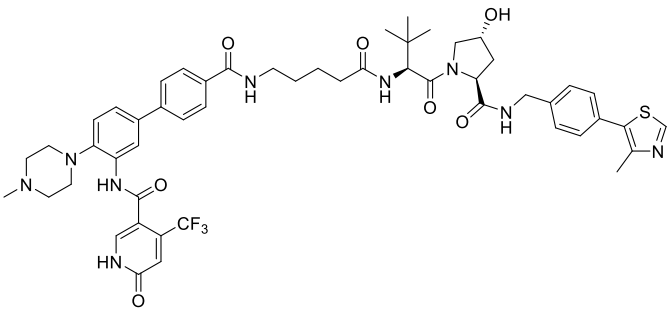
WDR5 is incorporated into Histone Lysine Methyltransferase complex MLL1 that is a crucial epigenetic writer to modify DNA accessibility. WDR5 was shown to be crucial to recruit the transcription factor MYC to chromatin. Both interaction partners are oncoproteins that are known to be strong drivers for lymphoid and leukaemia cancers (MLL1) and neuroblastoma (MYC). Their overexpression trigger substantial oncogenic programs or deregulate cell lineage differentiation mechanisms.

Summary

Chemical Probe Name	Homer
Negative control compounds	nc_WDR5 and nc_VHL
Target(s) (synonyms)	WDR5 (WD40-repeat containing protein 5)
Recommended *in vitro* assay concentration	< 1 µM for Homer, nc_WDR5 and nc_VHL; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	This chemical probe was not tested for *in vivo* use
Publications	PMID: 33980013
Orthogonal chemical probes	
In vitro assay(s) used to characterise	ITC
Cellular assay(s) for target-engagement	NanoBRET, HiBit, Immunoblotting, Proteomics, CHX, qPCR, rescue experiments, quantitative Proteomics
ChemicalProbes.org	

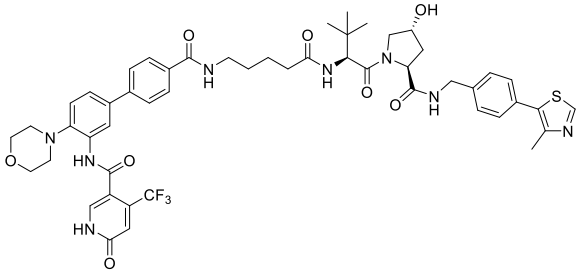
Chemical Probe & Negative Control Structures and Use

Homer



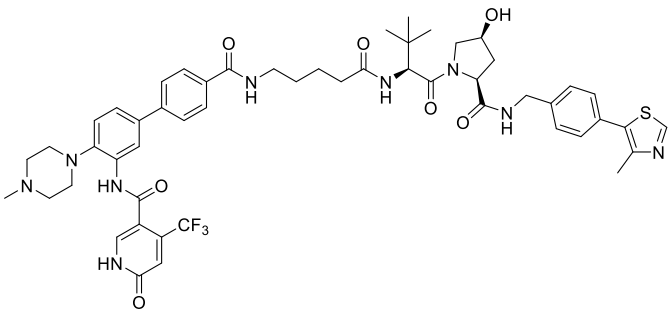
SMILES:
CC1=C(C2=CC=C(CNC([C@@H]3C[C@@H](O)CN3C([C@H](C(C)(C)C)NC(CCCCNC(C4=CC=C(C5=CC=C(N6CCN(C)CC6)C(NC(C7=CNC(C=C7C(F)(F)F)=O)=O)=C5)C=C4)=O)=O)=O)=O)C=C2)SC=N1
InChiKey: OFNZESNEBSQKSE-BQGOKDIQSA-N
Molecular weight: 1012.16
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 50 mM; use only 1 freeze/thaw cycle per aliquot

nc_WDR5



SMILES:
CC1=C(C2=CC=C(CNC([C@@H]3C[C@@H](O)CN3C([C@H](C(C)(C)C)NC(CCCC

nc_VHL



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InChiKey: BFXBMIZHEIFXOC-LTJJNQLXSA-N
Molecular weight: 999.12
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 50 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

Homer binds potently to WDR5 with a KD(ITC) of 18 nM. Selectivity was shown in proteome-wide studies.

Potency in Cells and Cellular Target Engagement:

Homer is non-toxic as demonstrated by the AlarmarBlue assay in U2OS cells. NanoBRET measurements showed an IC_{50} of 13.6 µM. The degradation of WDR5 in MV4-11 and HL-60 cells was achieved with a DC_{50} < 100 nM and DC_{max} of 58% at 1 µM, validated in HiBiT assay and by Western Blots. CHX assay, rescue experiments and qPCR showed proteasome-dependent mechanism of Homer. nc_WDR5 and nc_VHL showed no cellular activity.