

CCT369260: A Chemical Probe for BCL6

Version 1.0 (25th July 2022)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!/specificprobeoverview/CCT369260>

Overview

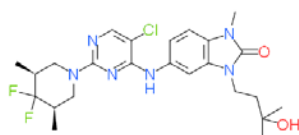
BCL6 is a zinc finger transcription factor. By binding to DNA and recruiting one of its co-repressors (NCoR, SMRT, or BCOR) to its dimeric BTB domain, BCL6 represses genes involved in cell cycle control, cell death, differentiation, and the DNA damage response. This results in B-cells in the germinal centre to proliferate rapidly, evade growth checkpoint controls, and tolerate high levels of DNA damage which is required for the process of somatic hypermutation of antibodies and may lead to lymphomagenesis.

Summary

Chemical Probe Name	CCT369260 (degrader)
Negative control compound	CCT393732
Target(s) (synonyms)	BCL6 (BCL6 transcription repressor, Zinc Finger Protein 51)
Recommended <i>in vitro</i> assay concentration	Use at concentration up to 1 μ M for CCT369260 and CCT393732; use with control and orthogonal probe for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Tested in female Balb/C mice with dosing at 1 mg/kg iv and 15 mg/kg po. A clear decrease in levels of BCL6 in the tumor was observed up to 10 h after dosing in a mouse OCI-Ly1 DLBCL xenograft model with single dose.
Publications	PMID: 32275432
Orthogonal chemical probes	TP-021
<i>In vitro</i> assay(s) used to characterise	TR-FRET
Cellular assay(s) for target-engagement	MSD (Meso Scale Discovery) degrader assay, Immunofluorescence-based BCL6 degradation assay in SUDHL-4 cells

Chemical Probe & Negative Control Structures and Use

CCT369260 Chemical Probe



SMILES:

C[C@H]1CN(C[C@@H](C)C1(F)F)c1ncc(c(Nc2ccc3c(c2)N(CCC(C)(C)O)C(N3C)=O)n1)[Cl]

InChIKey: VFNPUAOAEFMXQI-GASCZTMLSA-N

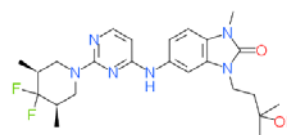
Molecular weight: 508.22 g/mol

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

CCT393732 Negative Control



SMILES:

C[C@H]1CN(C[C@@H](C)C1(F)F)c1nccc(Nc2ccc3c(c2)N(CCC(C)(C)O)C(N3C)=O)n1

InChIKey: MLRMGHITRSOINN-IYBDPMFKSA-N

Molecular weight: 474.26 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

Chemical Probe Profile

In vitro Potency & Selectivity:

CCT369260 is a proteasome dependent monovalent BCL6 degrader with IC₅₀ = 520 nM (TR-FRET). It is selective by proteomics vs 17 BTB/ZF domain proteins. Closest off-targets in the GPCR panel (48 targets at 10 μ M) (Ki [nM]) are OPRM1 (870), PBR (1100) and HRH3 (2300). The thermal shift SGC panel at 20 μ M (99 kinases and 3 bromodomains) is clean.

Potency in Cells and Cellular Target Engagement:

In the Meso Scale Discovery degrader assay DC₅₀ is 49 nM in OCI-Ly1 cell (full degrader) and 62 nM in Karpas 422 cells. DC₅₀ is the compound conc. at which 50% of endogenous BCL6 protein is degraded. In the immunofluorescence-based BCL6 degradation assay DC₅₀ is 90 nM in SUDHL-4 cells and D_{max} > 85 %. The proliferation assay gives the following results for GI₅₀ [nM]: OCILy1 cells (35), KARPAS (27), SUDHL-4 (92), OCI-Ly3 (1610).