

JNJ-4355: A Chemical Probe for MCL1

Version 1.0 (31st August 2023)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-4355>

Overview

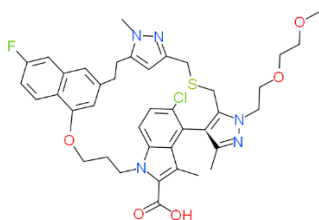
MCL1 is an anti-apoptotic protein, which is a member of the Bcl-2 family. MCL1 regulates mitochondrial integrity by blocking BAK/BAX oligomerization and pore formation. Alternative splicing results in multiple transcript variants. The longest gene product (isoform 1) enhances cell survival by inhibiting apoptosis while the alternatively spliced shorter gene products (isoform 2 and isoform 3) promote apoptosis and are death-inducing.

Summary

Chemical Probe Name	JNJ-4355
Negative control compound	JNJ-78732576
Target(s) (synonyms)	MCL1 apoptosis regulator, BCL2 family member (BCL2L3)
Recommended <i>in vitro</i> assay concentration	Use at concentration up to 10 μ M for JNJ-4355 and JNJ-78732576; use with control for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Tested in vivo: Tested in mouse and rat (dose IV bolus 1 mg/kg); JNJ-4355 disrupts MCL1 complexes in MOLM-13 (AML) human xenograft. A single 10 mg/kg IV bolus dose in mouse eradicates tumors for over 25 days.
Publications	None at time of writing, Patent: WO2021165370A1 , Abstract
<i>In vitro</i> assay(s) used to characterise	HTRF assay
Cellular assay(s) for target-engagement	Caspase Glo MOLP-8 assay

Chemical Probe & Negative Control Structures and Use

JNJ-4355 Chemical Probe



SMILES:

Cc1c2c3c(ccc2n(CCCOc2cc(CCc4cc(CSCc5c3c(C)nn5CCOCCOC)nn4C)cc3cc(ccc23)F)c1C(O)=O)[Cl]

InChiKey: LUVVOYGUFQRWXGQ-UHFFFAOYSA-N

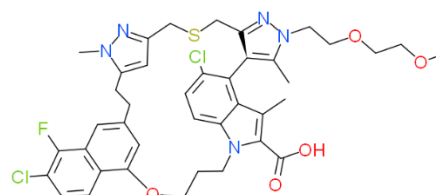
Molecular weight: 759.27 g/mol

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

JNJ-78732576 Negative Control



SMILES:

Cc1c2c3c(ccc2n(CCCOc2cc(CCc4cc(CSCc5c3c(C)nn5CCOCCOC)n5)nn4C)cc3c(c(cc23)[Cl])F)c1C(O)=O)[Cl]

InChiKey: VURAYLSMFLQNMM-UHFFFAOYSA-N

Molecular weight: 793.23 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:

JNJ-4355 is a potent MCL1 inhibitor with $K_i = 0.015$ nM (HTRF assay). It shows a good selectivity vs the closest related protein hBCL2 ($K_i > 3.75$ μ M) and other family members hBCL2A1 (BFL-1) ($K_i > 5$ μ M) and hBCL2L1BCL-XL ($K_i > 5$ μ M). Closest off-targets in the CEREP panel (76 targets) at 1 μ M (% inhibition) are Cl⁻ channel (GABA-gated) = 22.6%, hPTGS2(COX2) = 20.2%, hBZDp (TSPO) = 19,1 %.

Potency in Cells and Cellular Target Engagement:

For JNJ-4355 AC_{50} is 12 nM in the Caspase Glo MOLP-8 assay and 69 nM in the Caspase Glo KMS12PE assay. In the Caspase Glo KMS12PE KO assay $AC_{50} > 30$ μ M.