JNJ-8003: A Chemical Probe for RSV-L

Version 1.0 (23rd June 2025)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-8003

Overview

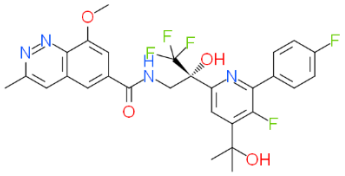
The RSV polymerase complex is composed of a large protein (L), which is a multidomain protein having RNA-dependent RNA polymerase (RdRp), polyribonucleotidyl transferase (PRNTase) or capping, and methyltransferase (MTase) activities, and 4 phosphoproteins. The RdRp domain is essential for transcription and replication of the viral RNA genome. The capping and the MTase domains contribute to the formation of capped and methylated mRNAs.

Summary

Chemical Probe Name	JNJ-8003
Negative control compound	JNJ-6643
Target(s) (synonyms)	RSV-L
Recommended *in vitro* assay concentration	Use at concentration ??? µM for JNJ-8003 and JNJ-6643; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in mice with up 100 mg/kg (po dose in PEG-400); Shows statistically significant and dose dependent reduction of viral load and viral RNA when tested in Balb-C mice.
Publications	PMID: 37865687,PMID: 39105710 (Cmp. 28)
In vitro assay(s) used to characterise	Biotinylated primer extension Flashplate assay, SPR
Cellular assay(s) for target-engagement	RSV sub-genomic replicon assay (APC-126 cells), Reporter assay

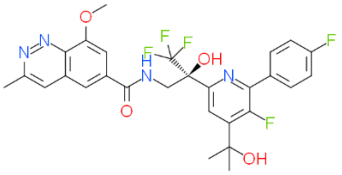
Chemical Probe & Negative Control Structures and Use

JNJ-8003 Chemical Probe



SMILES: Cc1cc2cc(cc(c2nn1)OC)C(NC[C@](c1cc(c(c(c2ccc(cc2)F)n1)F)C(C)(C)O)(C(F)(F)F)O)=O
InChiKey: XMOSIGSMKGYOBC-MHZLTWQESA-N
Molecular weight: 576.18 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-6643 Negative Control



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Chemical Probe Profile

In vitro Potency & Selectivity:

JNJ-8003 is a potent Inhibitor of RSV-L with IC_{50} = 0.67 nM in a biotinylated primer extension Flashplate assay that measures the inhibition of RNA synthesis activity of the recombinant RSV L + P, IC_{50} = 0.73 nM in a RSV L+P primer extension assay testing RNA-dependent RNA polymerase (RdRp) activity and ΔTm = 6 °C in a thermal shift assay using purified RSV L + P complex and Kd = 0.84 nM in SPR using RSV L + P complex. In a virus panel done with the reporter assay only minor activity was observed against the human metapneumovirus (CAN97-83a, EC_{50} = 88 nM), PIV-1 (Washington/20993/1964, EC_{50} = 13 µM), PIV-3 (JS, EC_{50} = 11 µM), VSV (Indiana, EC_{50} > 25 µM). Human polymerases were tested in various assays: DNA Pol α, DNA Pol β, DNA Pol γ, POLRMT, RNA Pol II (all IC_{50} > 100 µM). Closest off-targets in the Cerep panel (80 targets) are (IC_{50} [µM]): ADORA3(h) (49), BZDp(h) (0.56), Cl- channel (GABA-gated) (7.4), PTGER4(h) (1.3), TACR1(h) (8.4), TACR2(h) (6.8).

Potency in Cells and Cellular Target Engagement:

JNJ-8003 is also a potent inhibitor in the RSV sub-genomic replicon assay (APC-126 cells): EC_{50} = 0.15 nM and of RSV A2 replication in a reporter assay (HeLa cell-based using rgRSV224 reporter strain): EC_{50} = 0.78 nM.