JNJ-3738: A Chemical Probe for CDK7

Version 1.0 (18th June 2024)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-3738

Overview

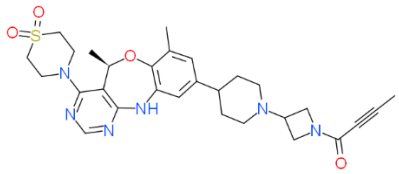
CDK7 controls RNA-Polymerase II transcription by phosphorylating serine 5 of RNA polymerase II C terminal repeats and CDK9. CDK7 regulates the cell cycle by functioning as the CDK activating kinase for CDK1, 2, 4 and 6.

Summary

Chemical Probe Name	JNJ-3738
Negative control compound	JNJ-6240
Target(s) (synonyms)	CDK7 (CDKN7, STK1)
Recommended *in vitro* assay concentration	Use at concentration up to 1 µM for JNJ-3738 and JNJ-6240; use with control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in mouse (IV 0.5 mpk (20% HPCD), PO 5 mpk (20% HPCD)), rat (IV 1 mpk (20% HPCD), PO 5 mpk (20% HPCD)) and dog (IV 1 mpk (20% HPCD), PO 5 mpk (20% HPCD)); leads to tumor growth inhibition in AML xenograft (Kasumi-1) at 10 mpk QD
Publications	None at time of publication
In vitro assay(s) used to characterise	Biochemical assay using CDK7/cyclinH/MAT1 complex
Cellular assay(s) for target-engagement	Detection of p-RNA pol II Ser 5 in A549 (WT CDK7) cells after 3 hrs incubation with probe; Antiproliferation assay using OCI AML3 cells

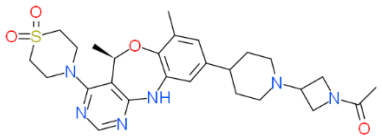
Chemical Probe & Negative Control Structures and Use

JNJ-3738 Chemical Probe



SMILES:CC#CC(N1CC(C1)N1CCC(CC1)c1cc(C)c2c(c1)Nc1c(c(ncn1)N1CCS(CC1)(=O)=O)[C@@H](C)O2)=O
InChiKey: OLEFHQBTXFCZON-HXUWFJFHSA-N
Molecular weight: 564.25 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-6240 Negative Control



SMILES:CC(N1CC(C1)N1CCC(CC1)c1cc(C)c2c(c1)Nc1c(c(ncn1)N1CCS(CC1)(=O)=O)[C@@H](C)O2)=O
InChiKey: VFSZSVNLAQBKOO-GOSISDBHSA-N
Molecular weight: 540.25 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-3738 is a potent irreversible covalent inhibitor of CDK7 with K^{I}_{app}= 31 nM and k_{inact}/K^{I}_{app} = 2603 M-1s-1 in a biochemical assay with CDK7/cyclinH/MAT1 complex. The ActivX screen with ~280 kinases shows good selectivity vs the CDK family [% inhibition]: CDK9 (49) vs CDK7 (95). Closest off-targets at 1 µM are CAMKK2 (70), MPSK1 (65). The DiscoverX KinaseScreen at 1 µM also shows good CDK selectivity: CDK7 > 99 % inh., CDK9 36 % inh. The CEREP panel at 10 µM is clean except for HRH1 (77% inh.). The closest off-target for the Proteome-wide Selectivity-activity-based protein profiling (ABPP) (Jurkat) is PTGES2 (67 % inh.).

Potency in Cells and Cellular Target Engagement:

The IC_{50} for the detection of p-RNA pol II Ser 5 in A549 (WT CDK7) cells after 3 hours incubation with JNJ-3738 is 58 nM and for the C312S mutant CDK7 > 10 µM. The antiproliferation assay with OCI AML3 cells results in an IC_{50} = 4 nM after 4 days.