JNJ-54119936: A Chemical Probe for RORC

Version 1.0 (20th October 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-54119936

Overview

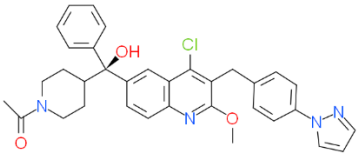
Nuclear hormone receptor (NHR), RORC is an immune cell-specific isoform of RORγ. It is a key transcription factor for the development of Th17 cells and the production of IL-17A, IL-17F and IL-22. It has both DNA (DBD) and ligand binding domains (LBD). The DBD confers gene target specificity while the LBD is the control switch for NHR function. IL-17 is implicated in several autoimmune and inflammatory diseases, and biologics targeting IL-23 and IL-17 have shown significant clinical efficacy in treating psoriasis and psoriatic arthritis.

Summary

Chemical Probe Name	JNJ-54119936
Negative control compound	JNJ-53721590
Target(s) (synonyms)	RORC (Retinoic Acid Related Orphan Receptor γT, NR1F3, RZRG, RORG, TOR)
Recommended *in vitro* assay concentration	Use at concentration up to 1 µM for JNJ-54119936 and JNJ-53721590; use with control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in rat with 1 mg/kg dose for i.v. and 5 mg/kg dose for p.o.
Publications	US20140107094A1
Orthogonal chemical probes	
In vitro assay(s) used to characterise	ThermoFluor Binding Assay
Cellular assay(s) for target-engagement	1-hybrid LBD, Human whole blood assay

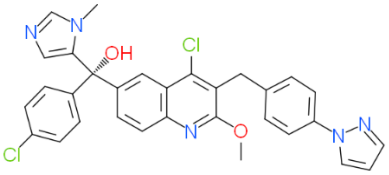
Chemical Probe & Negative Control Structures and Use

JNJ-54119936 Chemical Probe



SMILES:CC(N1CCC(CC1)[C@](c1ccccc1)(c1ccc2c(c1)c(c(Cc1ccc(cc1)n1cccn1)c(n2)OC)[Cl])O)=O
InChiKey: QBIGUDRHHJTXKG-UUWRZZSWSA-N
Molecular weight: 580.22 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

JNJ-53721590 Negative Control



SMILES:Cn1cncc1[C@](c1ccc(cc1)[Cl])(c1ccc2c(c1)c(c(Cc1ccc(cc1)n1cccn1)c(n2)OC)[Cl])O
InChiKey: UWOBQISTECYGOP-HKBQPEDESA-N
Molecular weight: 569.14 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-54119936 showed potent activity for the binding to RORC ligand binding domain, (TF qKD = 5.3 nM). It was not active against RORA and RORB (both: TF qKD > 75 µM). A nuclear receptor screen did not show significant ago-/antagonism at 3 µM. All targets tested in the Cerep panel (50 at 1 and 10 µM) and DiscoverX panel (50 kinases at 10 µM) showed < 50 % inhibition.

Potency in Cells and Cellular Target Engagement:

JNJ-54119936 is active in the one-hybrid LBD assay (IC_{50} = 30 nM; 100% inhibition at 6 µM) and the hWB assay (IC_{50} = 332 nM; 82 % inhibition at 10 µM).