JNJ-39758979: A Chemical Probe for HRH4

Version 1.0 (25th July 2022)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-39758979

Overview

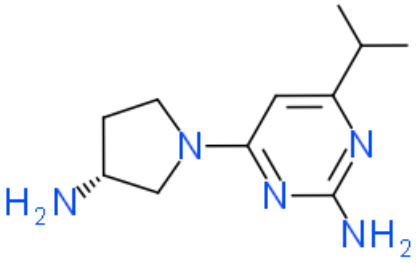
HRH4 is a GPCR that mediates chemotaxis of mast cells, eosinophils, dendritic cells, T cells, monocytes and NK cells and cytokine production from dendritic cells, CD4 + T cells, monocytes and NK T cells. It has been implicated in asthma, allergy, rheumatoid arthritis, atopic dermatitis, psoriasis, and other inflammatory diseases.

Summary

Chemical Probe Name	JNJ-39758979
Negative control compound	JNJ- 39668551
Target(s) (synonyms)	HRH4 (Histamine Receptor H4, GPCR105, H4R)
Recommended *in vitro* assay concentration	Use at conc. up to 10 µM for JNJ-39758979 and JNJ-39668551; use with control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in mice, rat and monkeys at various concentrations with good safety profile; reached clinical phase II
Publications	PMID: 2449<5018 (Compound 5), PMID: 24549371
In vitro assay(s) used to characterise	Binding assay (Membranes from SK-N-MC cells transfected with human H4 receptor)
Cellular assay(s) for target-engagement	Cell based cAMP Assay (pA2)

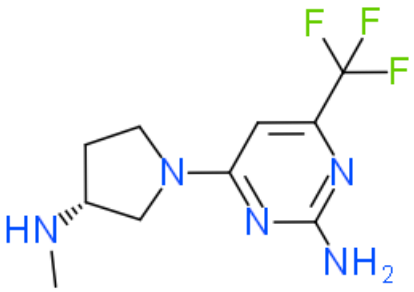
Chemical Probe & Negative Control Structures and Use

JNJ-39758979 Chemical Probe



SMILES: CC(C)c1cc(nc(N)n1)N1CC[C@H](C1)N
InChiKey: COOGVHJHSCBOQT-MRVPVSSYSA-N
Molecular weight: 221.16 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- 39668551 Negative Control



SMILES: CN[C@@H]1CCN(C1)c1cc(C(F)(F)F)nc(N)n1
InChiKey: ZSNJGYMDDSYJHS-ZCFIWIBFSA-N
Molecular weight: 261.12 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-39758979 shows potent activity on human HRH4 in a binding assay (Ki = 12.5 nM) and is < 50-fold selective within the target family (HRH3 (Ki = 1023 nM), HRH2 (Ki > 1 µM), HRH1 (Ki > 1 µM)). A kinase panel with 66 kinases is clean at 10 µM. The closest off-targets in a CEREP panel (50 targets at 1 µM) are CHRM1, CHRM2, CHRM3, CHRM4 (all Ki > 10 µM).

Potency in Cells and Cellular Target Engagement:

In a cell-based cAMP assay pA2 = 7.9 for human HRH4 (pA2 indicates the conc. of antagonist when double the agonist is required to have the same effect on the receptor as when no antagonist is present). JNJ-39758979 is active in an eosinophil shape change assay (PBMC and WB), a mast cell chemotaxis assay and a mouse ovalbumin challenge model for asthma.