JNJ-42226314: A Chemical Probe for MGLL

Version 1.0 (31st August 2023)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-42226314

Overview

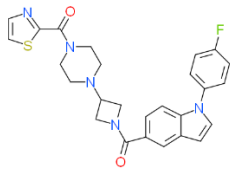
MGLL (serine hydrolase monoacylglycerol lipase) is the rate-limiting enzyme responsible for the degradation of the endocannabinoid 2-arachidonoylglycerol (2-AG) into arachidonic acid and glycerol. Inhibition of 2-AG degradation leads to elevation of 2-AG, the most abundant endogenous agonist of the cannabinoid receptors CB1 and CB2. Activation of these receptors has demonstrated beneficial effects on mood, appetite, pain, and inflammation.

Summary

Chemical Probe Name	JNJ-42226314
Negative control compound	JNJ-8034
Target(s) (synonyms)	MGLL (Monoglyceride lipase)
Recommended *in vitro* assay concentration	Use at concentration up to 10 µM for JNJ-42226314 and JNJ-8034; use with control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in vivo: i.p. dosing typically used in mouse; suitable for oral dosing in rat, dog; Intraperitoneal administration (30 mg/kg) inhibited [3H] SAR-127303 binding in the rat hippocampus, indicating brain penetration. Mouse dose-response study: The measured 50% effective dose (ED50) was 0.5 mg/kg (95% confidence interval, 0.4–0.7 mg/kg) (calculated plasma exposure: 51 ng/ml, brain exposure: 30 ng/g). Prolongs wakefulness in rats (30 mg/kg).
Publications	PMID: 31818916
In vitro assay(s) used to characterise	Fluorometric Assay (Inhibition of 4MU-B cleavage)
Cellular assay(s) for target-engagement	[3H] 2-OG cleavage activity assay

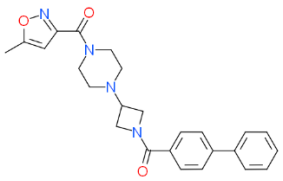
Chemical Probe & Negative Control Structures and Use

JNJ-42226314 Chemical Probe



SMILES: C1CN(CCN1C1CN(C1)C(c1ccc2c(ccn2c2ccc(cc2)F)c1)=O)C(c1nccs1)=O
InChiKey: IVOACCSOISMVBL-UHFFFAOYSA-N
Molecular weight: 489.16 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-8034 Negative Control



SMILES: Cc1cc(C(N2CCN(CC2)C2CN(C2)C(c2ccc(cc2)c2ccccc2)=O)=O)no1
InChiKey: CVQBGUIOFAMIJK-UHFFFAOYSA-N
Molecular weight: 430.20 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-42226314 is a potent MGLL inhibitor with IC_{50} < 5 nM (n=10) (Fluorometric Assay). A serine protease panel with 15 proteases tested at 10 µM is clean. The closest hit in a panel of endocannabinoid related targets is hFAAH with IC_{50} > 4 µM. All 50 targets in a kinase panel at 10 µM and 10 µM ATP show < 20% inhibition. Closest off-target in a CEREP panel (50 targets) at 10 µM is HTR1B (50% inhibition in a follow up assay).

Potency in Cells and Cellular Target Engagement:

JNJ-42226314 shows a good potency in the [3H] 2-OG cleavage activity assay [IC_{50} in nM]: 1.13 ± 0.05 (n> 10, human HeLa cells), 1.88 ± 0.41 (n = 6, human PBMC), 0.67 ± 0.11 nM (n = 9, mouse brain) and 0.97 ± 0.12 (n = 10, rat brain).