JNJ-42396302: A Chemical Probe for PDE10A

Version 1.0 (20th October 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/JNJ-42396302

Overview

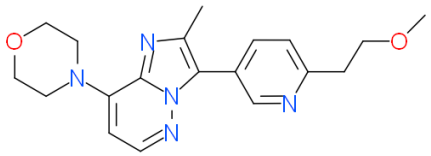
Phosphodiesterases (PDEs) are a family of enzymes encoded by 21 genes subdivided into 11 distinct families according to structural and functional properties. They are hydrolases that metabolically inactivate widely occurring intracellular second messengers, cAMP and cGMP, by catalytic hydrolysis of the 3'-ester bond, while forming the inactive 5'-monophosphate. The PDE families can be divided into three groups: (i) cAMP-specific; (ii) cGMP-specific; and (iii) dual-substrate PDEs of which PDE10A is a member. Although PDE10A is predominantly expressed in the brain, it is also expressed in neuroendocrine tissues.

Summary

Chemical Probe Name	JNJ-42396302
Negative control compound	JNJ-40573663
Target(s) (synonyms)	PDE10A (cAMP and cAMP-inhibited cGMP 3', 5'-cyclic phosphodiesterase 10A, Phosphodiesterase 10A1, PDE10)
Recommended *in vitro* assay concentration	Use at concentration up to 10 µM for JNJ-42396302 and JNJ-40573663; use with control and orthogonal probe for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in various animals: Dose-and time-dependent occupancy of rat brain PDE10 was shown with maximum occupancy 1 hour after p.o. dosing (ED50: 1.4 mg/kg).
Publications	WO2011051342A1
Orthogonal chemical probes	THPP-1
In vitro assay(s) used to characterise	SPA
Cellular assay(s) for target-engagement	Luciferase activity assay

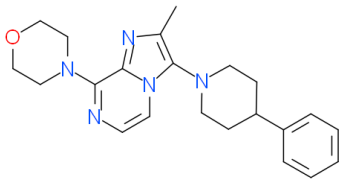
Chemical Probe & Negative Control Structures and Use

JNJ-42396302 Chemical Probe



SMILES: Cc1c(c2ccc(CCOC)nc2)n2c(c(ccn2)N2CCOCC2)n1
InChiKey: BPLVDYJDAVYLRQ-UHFFFAOYSA-N
Molecular weight: 353.19 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-40573663 Negative Control



SMILES: Cc1c(N2CCC(CC2)c2ccccc2)n2ccnc(c2n1)N1CCOCC1
InChiKey: DSSAFRSBYFWWMO-UHFFFAOYSA-N
Molecular weight: 377.22 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

Chemical Probe Profile

In vitro Potency & Selectivity:

JNJ-42396302 showed potent activity on human PDE10A ([^{3}H]cAMP substrate) with Ki = 13 nM (SPA) and inhibits cAMP and cGMP hydrolysis of isolated hPDE10A enzyme with IC_{50} = 40 nM for cAMP and IC_{50} = 51 nM for cGMP. PDE1B was the closest hit in a panel of PDEs is with Ki = 3.4 µM (257 fold). The CEREP receptor and enzyme panel (50) at 10 µM was clean. The Millipore kinase panel (230) at 10 µM showed < 50 % inhibition for all targets.

Potency in Cells and Cellular Target Engagement:

The concentration-dependent increase in luciferase activity in PDE10A CRE-Luc transfected HEK293 cells was 2.3 fold at 1 µM and 10 fold at 10 µM. In wild type HEK293 cells no increase in luciferase activity was measured at these concentrations.