BAY-7081: A Chemical Probe for PDE9A

Version 1.0 (4th September 2023)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BAY-7081

Overview

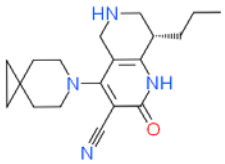
PDE9A is a very high-affinity cGMP-specific PDE believed to be a key regulator of cGMP levels. It catalyzes the hydrolysis of cAMP and cGMP to their corresponding monophosphates and is highly expressed in the kidney, brain, and spleen and to some extent in the heart. Under conditions of pathophysiology, the cGMP system can be suppressed, leading to, e.g., kidney diseases, cardiac insufficiency, hypertension, arteriosclerosis etc.

Summary

Chemical Probe Name	BAY-7081
Negative control compound	BAY-7424
Target(s) (synonyms)	PDE9A (Phosphodiesterase 9A)
Recommended *in vitro* assay concentration	Use at concentration of 1 µM for BAY-7081 and BAY-7424; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in vivo in rat (50mg/kg po) and dog. It is orally bioavailable. Tested in a urinary cGMP model, but a non-significant trend toward higher cGMP levels was observed at 40 mg/kg.
Publications	PMID: 36475653
In vitro assay(s) used to characterise	3H-cAMP and 3H-cGMP Scintillation Proximity Assay (SPA)
Cellular assay(s) for target-engagement	Cellular PDE9A assay

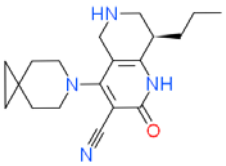
Chemical Probe & Negative Control Structures and Use

BAY-7081 Chemical Probe



SMILES: CCC[C@H]1CNCC2=C1NC(C(C#N)=C2N1CCC2(CC1)CC2)=O
InChiKey: NPPMVTBTTJNVKP-ZDUSSCGKSA-N
Molecular weight: 326.21 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

BAY-7424 Negative Control



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Chemical Probe Profile

In vitro Potency & Selectivity:

BAY-7081 shows potent activity in a SPA assay: human PDE9A (IC_{50} = 15 nM), mouse (IC_{50} = 34 nM), rat (IC_{50} = 42 nM). Selectivity against family members was tested in a PDE panel: Closest hit is PDE8A with IC_{50} = 1.49 µM. A Eurofins Panlabs panel with 75 targets at 10 µM and an in-house kinase panel with 31 kinases were clean.

Potency in Cells and Cellular Target Engagement:

In a cellular PDE9A assay EC_{50} was 995 nM for mouse PDE9A.