BAY 1753011: A Dual Probe for AVPR1A and AVPR2

Version 1.0 (9th January 2024)

Web link: https://www.sgc-ffm.uni-frankfurt.de/chemProbes#!specificprobeoverview/BAY%201753011

Overview

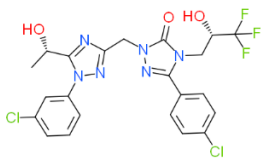
AVPR1A (V1a) subtype (a Gq coupled GPCR) mediates contraction of vascular smooth muscle cells in several different vascular beds including the vasa recta of the renal medulla and can stimulate hypertrophic and profibrotic signaling cascades in cardiac myocytes and fibroblasts. AVPR2 (V2), a Gs-coupled GPCR, is expressed on tubular cells of the distal convoluted and collecting ducts in kidney and Arginine vasopressin (AVP) stimulates the insertion of water channels, known as aquaporins, into the luminal membrane. As a result, AVP increases water retention and a reduction in serum osmolality. AVP is a 9 amino acid cyclic peptide hormone that plays a fundamental role in volume homeostasis.

Summary

Chemical Probe Name	BAY 1753011 (Pecavaptan)
Negative control compound	BAY-2297
Target(s) (synonyms)	AVPR1A (Arginine Vasopressin Receptor 1A), AVPR2 (Arginine Vasopressin Receptor 2)
Recommended *in vitro* assay concentration	Use at concentration of 100 nM for BAY 1753011 and BAY-2297; use with negative control for best interpretation of data; due to the high potency for oxytocin, use together with the oxytocin antagonist L-371,257 (Ki 4.6 nM).
Suitability for *in* vivo use and recommended dose	Good for in vivo use: BAY 1753011 (0.01 to 0.3 mg/kg; IV; single dose) protects from arginine vasopressin-mediated cardiac output in canine tachypacing-induced model of heart failure.
Publications	PMID: 31274842, PMID: 32946151, PMID: 33188886
In vitro assay(s) used to characterise	Radiometric AVPR1A (Eurofins #287530) and AVPR2 (Eurofins #287610) binding assays
Cellular assay(s) for target-engagement	Assay with bioluminescence detection

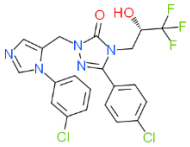
Chemical Probe & Negative Control Structures and Use

BAY 1753011 Chemical Probe



SMILES:
C[C@@H](c1nc(CN2C(N(C[C@@H](C(F)(F)F)O)C(c3ccc(cc3)[Cl])=N2)=O)nn1c1cccc(c1)[Cl])O
InChiKey: AZXOTZCWQDJCLY-SJCJKPOMSA-N
Molecular weight: 542.08 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-2297 Negative Control



SMILES:
C(c1cncn1c1cccc(c1)[Cl])N1C(N(C[C@@H](C(F)(F)F)O)C(c2ccc(cc2)[Cl])=N1)=O

InChiKey: QMCAUGCSTANBKK-SFHVURJKSA-N
Molecular weight: 497.06 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:

BAY 1753011 is a potent antagonist for AVPR1A (Ki = 0.5 nM) and AVPR2 (Ki = 0.6 nM) in the Eurofins binding assay. Ki > 10 µM for ADRA1B in a binding assay. There is a higher potency for the oxytocin receptor (Ki = 5.1 nM). Panlabs screen of >120 targets at 10 µM is clean. The closest off-target in the Eurofins kinase panel (378 kinases) at 10 µM is NEK3 (61% inhibition).

Potency in Cells and Cellular Target Engagement:

In a cell-based assay with bioluminescence detection IC_{50} is 3.6 nM for hAVPR1A and 1.7 nM for hAVPR2.