BAY-6672: A Chemical Probe for PTGFR

Version 1.0 (24th March 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BAY-6672

Overview

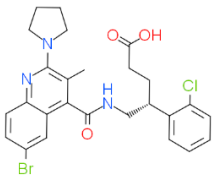
PTGFR is a GPCR that mediates the biological actions of PGF2α that plays a major role in the female reproductive system and the eye and is also a potent stimulator of smooth muscle constriction, vascular and bronchoconstriction where it contributes to acute and chronic inflammation. Furthermore, PTGFR/PGF2α is involved in cardiovascular conditions and pro-fibrotic processes. It facilitates bleomycin-induced pulmonary fibrosis independently of the pro-fibrotic mediator TGFβ.

Summary

Chemical Probe Name	BAY-6672
Negative control compound	BAY-403
Target(s) (synonyms)	PTGFR (prostaglandin F receptor, FP)
Recommended cell assay concentration	Use at concentration up to 500 nM for BAY-6672 and BAY-403; use with negative control for best interpretation of data
Suitability for *in* vivo use and recommended dose	A pulmonary fibrosis model (10 days silica-induced fibrosis) in mice with oral administration (3 -30 mg/ kg bid) showed a significant reduction of relevant pro-fibrotic and inflammatory biomarkers.
Publications	PMID: 32969660
Orthogonal chemical probes	
In vitro assay(s) used to characterise	Binding assay (Panlabs)
Cellular assay(s) for target-engagement	Bayer inhouse cell-based assay, functional cell-based assays: cytokine production in 3T3 fibroblasts and tissue contraction

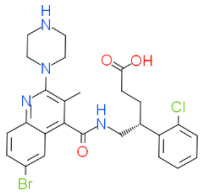
Chemical Probe & Negative Control Structures and Use

BAY-6672 Chemical Probe



SMILES:
Cc1c(C(NC[C@H](CCC(O)=O)c2ccccc2[Cl])=O)c2cc(ccc2nc1N1CCCC1)[Br]
InChiKey: YQOLEILXOBUDMU-KRWDZBQOSA-N
Molecular weight: 543.09
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-403 *Negative* Control



SMILES:
Cc1c(C(NC[C@H](CCC(O)=O)c2ccccc2[Cl])=O)c2cc(ccc2nc1N1CCNCC1)[Br]
InChiKey: ZZSNHHKTFMLWFY-KRWDZBQOSA-N
Molecular weight: 558.1
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-6672 shows potent activity in a Panlabs binding assay (IC_{50} = 22 nM; Ki = 16 nM) whereas the control BAY-403 exhibits no activity (EC_{50} > 10 µM). BAY-6672 has > 420-fold selectivity vs prostanoids EP1–EP4, IP, DP, CRTH2 based on Panlabs binding assays and 200-fold vs human TBXA2R (IC_{50} = 2.2 µM) based on a Panlabs cell-based assay. There are no off-targets in a Panlabs Profiling Screen of 77 targets.

Potency in Cells and Cellular Target Engagement:

BAY-6672 displays potent binding in a Bayer in-house cell-based assay (IC_{50} = 11 nM) and in functional cell-based assays (cytokine production (KC / MCP-1) in 3T3 fibroblasts: IC_{50} = 12 nM / 18 nM and a rat tissue contraction assay: IC_{50} = 52 nM).