BI-2081: A Chemical Probe for FFAR1

Version 1.0 (29th June 2022)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BI-2081

Overview

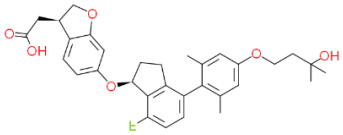
FFAR1 is a Gq-coupled GPCR strongly expressed in the pancreas with a weaker expression in brain. Activation of FFAR1 through medium to long chain saturated and unsaturated fatty acids (C12-C20) leads to an increase of intracellular Ca^{2+} concentrations via the IP3 pathway and stimulates the insulin release in the presence of glucose. It might be a target for Type 2 diabetes.

Summary

Chemical Probe Name	BI-2081
Negative control compound	BI-0340
Target(s) (synonyms)	FFAR1 (free fatty acid receptor 1), GPR40
Recommended *in vitro* assay concentration	Use at concentration of about 200 nM for BI-2081 and BI-0340; use with control and orthogonal probe for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in rats with oral (10 mg/kg) and intravenous (1 mg/kg) administration. Shows high bioavailability and strong glucose lowering effect and increase of the plasma insulin level in male Zucker diabetic fatty (ZDF) rats compared to untreated ZDF rats.
Publications	None at time of writing
Orthogonal chemical probes	TP-051
In vitro assay(s) used to characterise	FFAR1 biochemical assay
Cellular assay(s) for target-engagement	Human IPOne assay: Stimulation of 1321N1 cells expressing FFAR1 followed by measurement of the IP1 accumulation by fluorescence

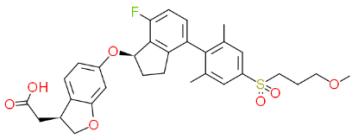
Chemical Probe & Negative Control Structures and Use

BI-2081 Chemical Probe



SMILES: Cc1cc(cc(C)c1c1ccc(c2c1CC[C@H]2Oc1ccc2c(c1)OC[C@H]2CC(O)=O)F)OCCC(C)(C)O
InChiKey: VXNAMCLMCBLNOL-NFQMXDRXSA-N
Molecular weight: 534.24 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

BI-0340 Negative Control



SMILES: Cc1cc(cc(C)c1c1ccc(c2c1CC[C@H]2Oc1ccc2c(c1)OC[C@H]2CC(O)=O)F)S(CCCOC)(=O)=O
InChiKey: PHYBFLAZLZLAGT-NFQMXDRXSA-N
Molecular weight: 568.19 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

Chemical Probe Profile

In vitro Potency & Selectivity:

BI-2081 shows potent activity on FFAR1 (Ki = 23 nM). 44 GPCRs from a Eurofins Safety Panel were tested at 10 µM and the closest off-targets are (Kd [µM]) ADRA2C (0.840), ADRA2A (1.3), CHRM3 (2.9), HRH1 (3.1), PTGER4 (4.6) and ADRA2B (21). From the 29 receptor/channel targets at 10 µM the closest off-targets (Kd [µM]) are PPARG (0.470) and THRA (rat, 3.5).

Potency in Cells and Cellular Target Engagement:

In the IPOne assay the EC_{50} was between 3 and 5 nM depending on assay conditions.