BI-5121: A Chemical Probe for HCRTR1

Version 1.0 (23rd June 2025)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BI-5121

Overview

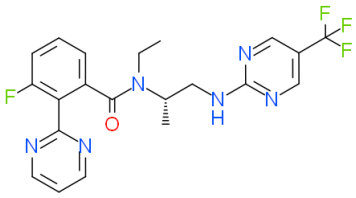
HCRTR1 is a GPCR involved in regulating arousal, wakefulness, and appetite through its high affinity for orexin-A. This receptor plays a significant role in the central nervous system Its dysregulation is linked to sleep disorders like narcolepsy and certain addictive behaviours.

Summary

Chemical Probe Name	BI-5121
Negative control compound	BI-6199
Target(s) (synonyms)	HCRTR1 (OX1)
Recommended *in vitro* assay concentration	Use at concentration of 100 nM for BI-5121 and BI-6199; use with control for best interpretation of data
Suitability for *in* vivo use and recommended dose	Tested in vivo in rats (i.v.,p.o. dose 4.5 mg/kg) and mice (i.v. dose 4.5 mg/kg, p.o. 2 mg/kg), suggested is oral dose. Oral administration of the compound at 0.1 -1mg/kg dose-dependently reduced premature responses in the 5CSRTT (5-choice serial reaction time impulsivity task) in Lister Hooded.
Publications	None at time of writing
In vitro assay(s) used to characterise	Eurofins radio-displacement assay (HCRTR1 binding)
Cellular assay(s) for target-engagement	Functional assay (OX1 ANTA IP1)

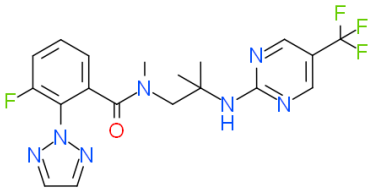
Chemical Probe & Negative Control Structures and Use

BI-5121 Chemical Probe



SMILES: CCN(C(c1cccc(c1c1ncccn1)F)=O)[C@@H](C)CNc1ncc(cn1)C(F)(F)F
InChiKey: MMHYOHYLSFWJJB-ZDUSSCGKSA-N
Molecular weight: 448.16 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-6199 Negative Control



SMILES: CC(C)(CN(C)C(c1cccc(c1n1nccn1)F)=O)Nc1ncc(cn1)C(F)(F)F
InChiKey: ODQDVAHMMNFXKP-UHFFFAOYSA-N
Molecular weight: 437.16 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-5121 is a potent antagonist of human HCRTR1 in the Eurofins radio-displacement binding assay with IC_{50} < 3 nM. There is a > 40-fold selectivity for HCRTR2 binding in the same assay (IC_{50} = 140 nM). In the OX2 (HCRTR2) ANTA IP1 functional assay IC_{50} = 62.6 nM (> 39-fold selectivity). The GPCR screen (44 targets) is clean (OPRK1: IC_{50} = 730 nM, > 200-fold selectivity). The Eurofins SafteyScreen (47 targets) at 10 µM is clean.

Potency in Cells and Cellular Target Engagement:

In the functional OX1 ANTA IP1 assay IC_{50} = 1.6 nM.