GSK046: A BD2 selective inhibitor of BRD2, BDR3, BRD4, BRDT family

Version 1.0 (24th March 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/GSK046

Overview

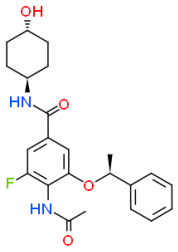
Proteins of the bromodomain and extra-terminal (BET) domain family – BRD2, BRD3, BRD4 and BRDT - are epigenetic readers that bind acetylated histones through their bromodomains to regulate gene transcription. BET family of bromodomains (BRDs) are well-known drug targets for many human diseases. The active pockets of the two tandem bromodomains BD1/BD2 are highly conserved (sequence similarity is about 95%), thus it is of great medical importance and still a significant challenge to develop BD1/BD2 selective inhibitors.

Summary

Chemical Probe Name	GSK046 (aka iBET-BD2)
Negative control compound	NA
Target(s) (synonyms)	BRD2/ Bromodomain-containing protein 2/KIAA9001/RING3; BRD3/ Bromodomain-containing protein 3/KIAA0043/RING3L; BRD4/ Bromodomain-containing protein 4/HUNK1; BRDT/ Bromodomain testis-specific protein/CT9
Recommended cell assay concentration	Use at concentrations up to 10 µM. We recommend to test at various concentrations with a 9 point curve starting from 10 µM down in 1/3 serial dilutions.
Suitability for *in* vivo use and recommended dose	Tested in rat and dog; 10 mg/kg (GSK620 recommended)
Publications	PMID: 32691591 (compound 59); PMID: 32193360; 33662213
Orthogonal chemical probes	GSK973, GSK620
In vitro assay(s) used to characterise	TR-FRET, BROMOscan
Cellular assay(s) for target-engagement	Cellular mechanistic assay – MCP-1 production

Chemical Probe & Negative Control Structures and Use

GSK046 Chemical Probe



SMILES:
CC(Nc1c(cc(cc1F)C(N[C@H]1CC[C@@H](CC1)O)=O)O[C@@H](C)c1ccccc1)=O
InChiKey: FRBRZGLUFOZRGD-JVPBZIDWSA-N
Molecular weight: 414.2
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.
DMSO stocks should be aliquoted in single-use volumes (and not re-frozen).
DMSO stocks older than 3-6 months should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM.

NA

Chemical Probe Profile

In vitro Potency & Selectivity:

BET TR-FRET assay: BRD2 (BD1) pIC50 = 5 (BD2) 6.6; BRD3 (BD1) pIC50 = 4.4 (BD2) 7.0; BRD4 (BD1) pIC50 = 4.2 (BD2) 7.3; BRDT (BD1) pIC50 < 4.3 (BD2) 6.7

BROMOScan (DiscoverX): BRD2(1): Kd = 1621 nM; (BD2) 35 nM; BRD3(1): Kd = 2082 nM; (BD2) 32 nM; BRD4(1): Kd = 769 nM; (BD2) 9 nM; BRDT(1): Kd = 2454 nM; (BD2) 15 nM.

Within target family: BROMOScan (DiscoverX) (40 tested): clean

Outside target family: Selectivity screen (48 targets tested): clean

Potency in Cells and Cellular Target Engagement:

Inhibits MCP-1 production (pIC50 = 7.5, IC50 = 30 nM) in an LPS-stimulated peripheral blood mononuclear cell (PBMC) cellular assay.