GSK620: A BD2 selective inhibitor of BRD2, BDR3, BRD4, BRDT

Version 1.0 (24th March 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/GSK620

Overview

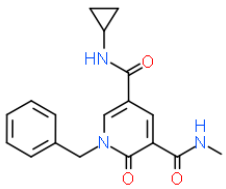
Proteins of the bromodomain and extra-terminal (BET) domain family – BRD2, BRD3, BRD4 and BRDT - are epigenetic readers that bind acetylated histones through their bromodomains to regulate gene transcription. BET family of bromodomains (BRDs) are well-known drug targets for many human diseases. The active 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	GSK620
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	Suitable: rat (IV 1mg/kg; PO 3 mg/kg); dog (IV 0.5 mg/kg; PO 1 mg/kg)
Publications	PMID: 32702236 (compound 20); PMID: 33662213
Orthogonal chemical probes	GSK046, GSK973
In vitro assay(s) used to characterise	TR-FRET, BROMOscan, SPR
Cellular assay(s) for target-engagement	Cellular mechanistic assay – LPS stimulated MCP-1 production

Chemical Probe & Negative Control Structures and Use

GSK620 Chemical Probe



SMILES: CNC(C1=CC(=CN(Cc2ccccc2)C1=O)C(NC1CC1)=O)=O
InChiKey: QZZCUOVXHPAQRQ-UHFFFAOYSA-N
Molecular weight: 325.1

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:

LPS-stimulated peripheral blood mononuclear cell (PBMC) cellular assay: stimulation of cytokines and chemokines, including monocyte chemoattractant protein 1 (MCP-1/CCL2). LPS-PBMC assay (MCP-1) pIC50= 7.2 ±0.3 (n=88); LPS-hWB (MCP-1) pIC50= 6.1 ±0.2 (n=8)