GSK973: A BD2 selective inhibitor of BRD2, BDR3, BRD4, BRDT

Version 1.0 (19th April 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/GSK973

Overview

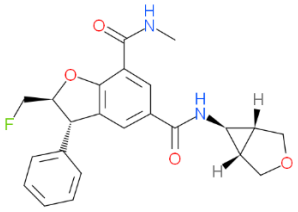
Proteins of the bromodomain and extra-terminal (BET) domain family – BRD2, BRD3, BRD4 and BRDT - are epigenetic readers that bind acetylated histones through their bromodomains to regulate gene transcription. BET family of bromodomains (BRDs) are well-known drug targets for many human diseases. The active 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	GSK973
Negative control compound	GSK943
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. 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, shows excellent pharmacokinetics in dog with low blood clearance, good oral bioavailability, and a moderate half-life.
Publications	PMID: 32832027 (compound 36)
Orthogonal chemical probes	GSK046, GSK620
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

GSK973 Chemical Probe

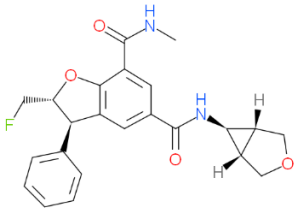


SMILES: [H][C@@]12COC[C@@]2([H])[C@@H]1NC(c1cc(C(NC)=O)c2c(c1)[C@H](c1ccccc1)[C@@H](CF)O2)=O
InChiKey: WZQLVEPIBAOOGF-RMMWZPCPSA-N
Molecular weight: 410.16

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.

GSK-943 Negative Control



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Chemical Probe Profile

In vitro Potency & Selectivity: Within target family: BROMOScan (DiscoverX) (34 tested): selective for the BD2 domain of BET proteins; Outside target family: Selectivity screen (48 targets tested): clean; Enantiomer GSK943 BET mutant TR-FRET assay: BRD4 (BD1) pIC_{50} < 4.3; (BD2) = 5.1

	BRD2	BRD3	BRD4	BRDT
BET TR-FRET (BD1) pIC50	4.4	4.5	4.6	4.5
BET TR-FRET (BD2) pIC50	7.5	7.8	7.8	7.4
BROMOScan (BD1) pKd	5.3	5.2	5.6	5.4
BROMOScan (BD2) pKd	8.3	8.5	8.7	8.3
SPR (BD1) Kd [nM]			>3000	
SPR (BD2) Kd [nM]			34	

Potency in Cells and Cellular Target Engagement: LPS-stimulated peripheral blood mononuclear cell (PBMC) cellular assay: MCP-1 pIC_{50}= 7.3