GSK789: A BD1 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/GSK789

Overview

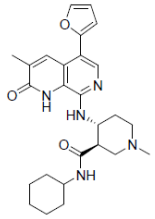
Proteins of the bromodomain and extra-terminal (BET) domain family – BRD2, BRD3, BRD4 and BRDT - are epigenetic readers that bind acetylated histones through their bromodomains to regulate gene transcription. BET family of bromodomains (BRDs) are well-known drug targets for many human diseases. The active 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	GSK789
Negative control compound	GSK791
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 1 µM. We recommend to test at various concentrations with a 9 point curve starting from 1 µM down in 1/3 serial dilutions.
Suitability for *in* vivo use and recommended dose	Tested in mice by IP administration; 10 mg/kg
Publications	PMID: 32787145 (compound 42)
Orthogonal chemical probes	GSK778
In vitro assay(s) used to characterise	TR-FRET; BROMOScan; chemoproteomics
Cellular assay(s) for target-engagement	Cellular mechanistic assay – antiproliferative and cytokine release

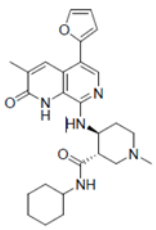
Chemical Probe & Negative Control Structures and Use

GSK789 Chemical Probe



SMILES:
CC1=NOC(C)=C1C2=C(OC[C@@H]3CNCC3)C=C4C5=C(N=C(COC)N5[C@H](C)C6=CC=CC=C6)C=NC4=C2
InChiKey: ZORLJXWXFABTPZ-CTNGQTDRSA-N
Molecular weight: 511.3
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.

GSK791 *Negative* Control



SMILES:
CC1=Cc2c(cnc(c2NC1=O)N[C@H]1CCN(C)C[C@@H]1C(NC1CCCCC1)=O)c1ccco1
InChiKey: NDEORODKVUYMFQ-SFTDATJTSA-N
Molecular weight: 432.3
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.

Chemical Probe Profile

In vitro Potency & Selectivity:

Within target family: BROMOScan (DiscoverX) (34 tested): Closest hit: TAF1 (BD2) pKd = 7.2 (pIC50 = 7.3; TR-FRET: pIC50 = 5) Outside target family: In-house panel (40 targets, data not shown)

Potency in Cells and Cellular Target Engagement:

Potent antiproliferative activity in various cancer cell lines: MV-4–11: IC50 = 125 nM; HL60: IC50 = 390 nM; THP-1: IC50 = 258 nM; Cytokine release - TNF alpha: 0.87µM, MCP-1: 0.67 µM, IL-6: 3.55 µM