GSK778: 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/BAY-069

Overview

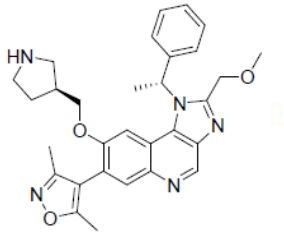
Proteins of the bromodomain and extra-terminal (BET) domain family – BRD2, BRD3, BRD4 and BRDT - are epigenetic readers that bind acetylated histones through their bromodomains to regulate gene transcription. BET family of bromodomains (BRDs) are well-known drug targets for many human diseases. The active 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	GSK778 (aka iBET-BD1)
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 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	Suitable; 15 mg/kg (s.c. BID)
Publications	PMID: 32787145 (compound 62)
Orthogonal chemical probes	GSK789
In vitro assay(s) used to characterise	FRET, BROMOscan, SPR
Cellular assay(s) for target-engagement	Cellular mechanistic assay – LPS-stimulated MCP-1 release; anti-proliferation in MV-4-11 and HL-60.

Chemical Probe & Negative Control Structures and Use

GSK778 Chemical Probe



SMILES: Cc1ccccc1Oc1cc(c2ccccc2c1[Cl])N1C(C=C(C(F)(F)F)NC1=O)=O
InChiKey: UNSHMXUHOHBLIQ-UHFFFAOYSA-N
Molecular weight: 446.06

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:

Excellent selectivity against other BCPs (Bromoscan)

Outside target family: Selectivity screen (50 targets tested): Closest hits are CHRNA1 (pIC50 = 6) and Cytochrome P450 3A4 (pIC50 = 6). BROMOScan (DiscoverX): BRD2(1): Kd = 13 nM, BRD3(1): Kd = 5 nM, BRD4(1): Kd = 5.9 nM, BRDT(1): Kd = 18 nM, SPR BRD4 (BD1): pKd= 8.0; BRD4 (BD2) pKd = 5.9.

Potency in Cells and Cellular Target Engagement: GSK778 engages the target in HEK293 cells: pIC50 = 7.3; Cell proliferation assay with the AML cell line MV-4−11 that has a MLL-AF4 rearrangement (3 days): growth inhibition with pIC50 = 7.0