

FHT-2344: A Chemical Probe for SMARCA2/4

Version 1.0 (6th February 2023)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/FHT-2344>

Overview

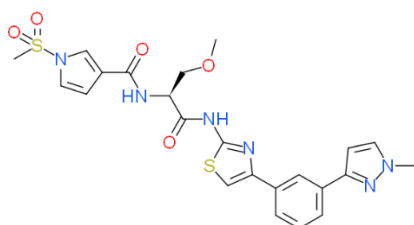
[SMARCA2/](#) [SMARCA4](#) are two closely related DNA-dependent ATPases that belong to the SNF2 superfamily. Their enzymatic activity is essential for the mechanical movement of nucleosomes and is therefore key to controlling gene transcription and DNA damage repair. Since they are critical in the regulation of cellular differentiation and proliferation, they are implicated in cancer and other diseases.

Summary

Chemical Probe Name	FHT-2344
Negative control compound	FHT-5908
Target(s) (synonyms)	SMARCA2/ SMARCA4 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2/4)
Recommended <i>in vitro</i> assay concentration	Use at concentration up to 1 μ M for FHT-2344 and FHT-5908; use with control for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Tested in 6-7 week old, female nude mice dosed daily with up to 20 mg/kg FHT-2344 by oral gavage
Publications	None at time of writing
<i>In vitro</i> assay(s) used to characterise	Measurement of the ATPase catalytic activity using the ADP-Glo™ detection reagent
Cellular assay(s) for target-engagement	Luciferase reporter assay

Chemical Probe & Negative Control Structures and Use

FHT-2344 Chemical Probe



SMILES:

Cn1ccc(c2cccc(c2)c2csc(NC([C@H](COC)NC(c3ccn(c3)S(C)(=O)=O)=O)n2)n1

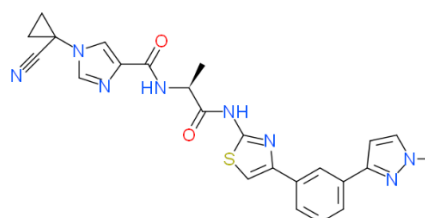
InChiKey: APLVGTKXOIMODQ-IBGZPJMESA-N

Molecular weight: 528.13 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

FHT-5908 Negative Control



SMILES:

C[C@@H](C(Nc1nc(cs1)c1cccc(c1)c1ccn(C)n1)=O)NC(c1cn(cn1)C1(CC1)C#N)=O

InChiKey: DMEDHHKXKVEBDF-HNNXBMFYSA-N

Molecular weight: 486.16 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

FHT-2344 is a potent SMARCA2 (IC₅₀ = 13.8 nM) and SMARCA4 (IC₅₀ = 26.1 nM) inhibitor (ATPase catalytic activity measurement). It shows a good selectivity vs CHD4 (IC₅₀ > 200 μ M). The GPCR scan and the DSF panel (104 targets) is clean.

Potency in Cells and Cellular Target Engagement:

FHT-2344 was used in the Luciferase reporter assay: The SMARCA2 transcriptional activity in a SMARCA4-mutant cell line results in an IC₅₀ = 29.8 nM and the SMARCA4 transcriptional activity in a SMARCA2-mutant cell line yields an IC₅₀ = 30.2 nM.