MRIA9: A Chemical Probe for SIK

Version 1.0 (5th July 2021)

Web link for more details: https://www.thesgc.org/chemical-probes/MRIA9

Overview

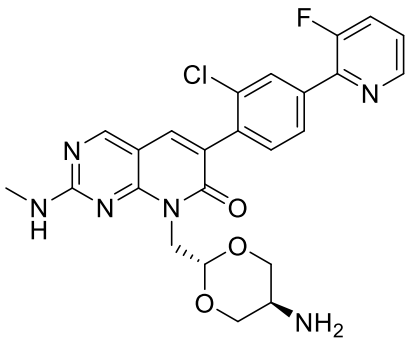
Salt-inducible kinases (SIK1-3) are members of the AMP activated protein kinase (AMPK) sub-family of the calcium/ calmodulin-dependent kinase (CaMK) group. These serine/ threonine kinases act as regulators of energy homeostasis and metabolic stress. In addition to the key function of SIK in regulating metabolism, an imbalance in SIK has been observed in the context of several diseases, especially in cancer, with both tumor-promoting and tumor suppressive roles being reported.

Summary

Chemical Probe Name	MRIA9
Negative control compound	MR7
Target(s) (synonyms)	SIK (Salt-Inducible Kinase 1, 2 and 3)
Recommended cell assay concentration	Use at concentration of 1 µM (and < 10 µM) for MRIA9 and MR7; use with control for best interpretation of data.
Suitability for *in* vivo use and recommended dose	MRIA9 was not tested in vivo.
Publications	PMID: 34086472
Orthogonal chemical probes	
In vitro assay(s) used to characterise	DSF, Radiometric inhibition assay
Cellular assay(s) for target-engagement	NanoBRET™

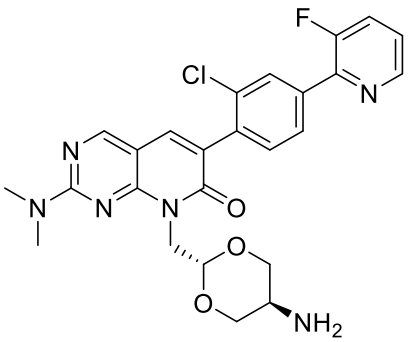
Chemical Probe & Negative Control Structures and Use

MRIA9 Chemical Probe



SMILES:
CNC1=NC=C2C(N(C[C@H]3OC[C@H](N)CO3)C(C(C4=CC=C(C5=NC=CC=C5F)C=C4Cl)=C2)=O)=N1
InChiKey: QKNBRNSGPNCARD-SGNKCFNYSA-N
Molecular weight: 496.93
Storage Stable as solid in the dark at -20°C. NB making aliquots rather than freeze-thawing is recommended
Dissolution: Soluble in DMSO up to 50 mM; use only 1 freeze/thaw cycle per aliquot

MR7 Negative Control



SMILES:
CN(C)C1=NC=C2C(N(C[C@H]3OC[C@H](N)CO3)C(C(C4=CC=C(C5=NC=CC=C5F)C=C4Cl)=C2)=O)=N1
InChiKey: RRFFBKGCCWPMLK-OQIWPSSASA-N
Molecular weight: 510.95
Storage: Stable as solid in the dark at -20°C. NB making aliquots rather than freeze-thawing is recommended
Dissolution: Soluble in DMSO up to 50 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

MRIA9 shows potent activity on SIK1, SIK2 and SIK3 with a IC_{50} of 55, 48 and 22 nM respectively on the radiometric assay ^{33}PanQinase Activity Assay at 3 µM, 1 µM and 1 µM ATP concentration respectively for each kinase. MRIA9 has been shown to be selective in a ^{33}PanQinase activity assay from Reaction Biology at 1 µM. The closest off-target was PAK2 (IC_{50} = 41 nM), PAK3 (IC_{50} = 140 nM) and

Potency in Cells and Cellular Target Engagement:

In NanoBRET assay using HEK293T cells MRIA9 binds SIK1, SIK2 and SIK3 with an IC_{50} of 516, 180 and 23nM respectively. In the full NCI-60 panel MRIA9 showed no significant cell toxicity as well as growth inhibition in a single high dose of 1 µM in the full NCI-60.