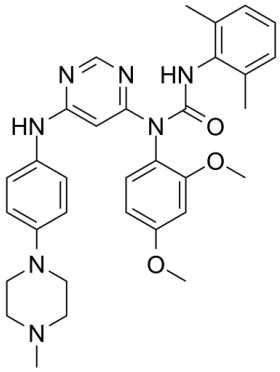
Data Sheet

Product Name:	HG-9-91-01
Cat. No.:	CS-1749
CAS No.:	1456858-58-4
Molecular Formula:	C32H37N7O3
Molecular Weight:	567.68
Target:	Salt-inducible Kinase (SIK)
Pathway:	Immunology/Inflammation
Solubility:	DMSO : ≥ 150 mg/mL (264.23 mM)



BIOLOGICAL ACTIVITY:

HG-9-91-01 is a potent and highly selective salt-inducible kinase (**SIK**) inhibitor with **IC_{50}**s of 0.92 nM, 6.6 nM and 9.6 nM for **SIK1**, **SIK2** and **SIK3** respectively. IC50 & Target: IC50: 0.92/6.6/9.6 nM (SIK1/2/3)[1] **In Vitro:** HG-9-91-01 inhibits a number of protein tyrosine kinases that possess a threonine residue at the gatekeeper site, such as Src family members (Src, Lck, and Yes), BTK, and the FGF and Ephrin receptors[1]. HG-9-91-01 demonstrates a strong correlation between the potency of SIK2 inhibition and enhanced IL-10 production. In agreement with these reports, pretreating BMDCs with HG-9-91-01, a recently described inhibitor of SIK1-3, along with several other kinases, results in concentration-dependent potentiation of zymosan-induced IL-10 production with an EC_{50} ~200 nM and a maximum effect similar to that observed with PGE_2[2]. HG-9-91-01 has more than a 100-fold greater potency against SIKs than AMPK (IC_{50}=4.5 μM) in a cell-free assay. HG-9-91-01 treatment dose dependently increased mRNA expression of Pck1 and G6pc and that effect is similar in cells treated with 4 μM HG-9-91-01. Consistent with this observation, there is also a dose-dependent increase in glucose production following HG-9-91-01 treatment[3].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: HG-9-91-01 is dissolved in DMSO and stored, and then diluted with appropriate media before use[2].[2]Bone marrow is harvested from femurs and tibias of C57BL/6 mice. Bone-marrow-derived dendritic cells (BMDCs) are differentiated DMEM. Cultures are differentiated for 7 d and routinely analyzed for >90% CD11c (allophycocyanin (APC) anti-CD11c clone HL3) positivity by flow cytometry before use in experiments. Lentiviral transduction of bone marrow cultures is conducted by addition of 293T culture supernatants containing lentiviral particles encoding the CREB-dependent luciferase reporter construct or CRTC3 targeting or control shRNAs 1 d postisolation. Stable integration of lentiviral shRNA constructs is selected by addition of puromycin (3 μg/mL) on day 4 posttransduction. After 2 d, stably transduced BMDCs are released from selection and used in subsequent assays. Unless otherwise indicated, cells are treated for 2 d with PGE2 (5 μM) or HG-9-91-01 (0.5 μM) or an equivalent concentration of DMSO (≤0.5%) and then stimulated for 18 h with LPS (100 ng/mL), R848 (10 μg/mL), or Zymosan (4 μg/mL)[2].

References:

[1]. Clark K, et al. Phosphorylation of CRTC3 by the salt-inducible kinases controls the interconversion of classically activated andregulatory macrophages. Proc Natl Acad Sci U S A. 2012 Oct 16;109(42):16986-91.

[2]. Sundberg TB, et al. Small-molecule screening identifies inhibition of salt-inducible kinases as a therapeutic strategy to enhance immunoregulatory functions of dendritic cells. Proc Natl Acad Sci U S A. 2014 Aug 26;111(34):12468-73.

[3]. Patel K, et al.The LKB1-salt-inducible kinase pathway functions as a key gluconeogenic suppressor in the liver. Nat Commun. 2014 Aug 4;5:4535.

CAIndexNames:

Urea, N-(2,4-dimethoxyphenyl)-N'-(2,6-dimethylphenyl)-N-[6-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl]-

SMILES:

CC1=CC=CC(C)=C1NC(N(C2=NC=NC(NC3=CC=C(N4CCN(C)CC4)C=C3)=C2)C5=CC=C(OC)C=C5OC)=O

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