

Product Data Sheet

Product Name: D4476
Cat. No.: GC13202

Chemical Properties

Cas. No. 301836-43-1

Chemical Name 4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-pyridin-2-yl-1H-imidazol-2-yl]benzamide

SMILES C1COC2=C(O1)C=CC(=C2)C3=C(NC(=N3)C4=CC=C(C=C4)C(=O)N)C5=CC=CC=N5

Formula $C_{23}H_{18}N_4O_3$ M.Wt 398.41

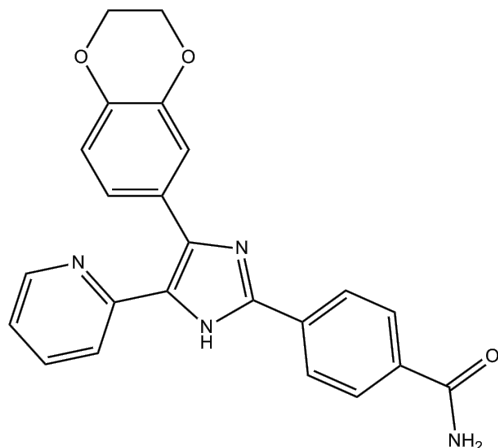
Solubility ≥ 19.9 mg/mL in DMSO, ≥ 41.5 mg/mL in EtOH with ultrasonic and warming

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1,2]:

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Cell lines H4IIE, HeLa and HCT116 cell lines

Preparation method The solubility of this compound in DMSO is >19.9 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition H4IIE: 0-150 µM for 1 h; HeLa: 50 µM; HCT116: 5-40 µM for 48 h

Applications In H4IIE hepatoma cells, D4476 specifically inhibited the phosphorylation of endogenous forkhead box transcription factor O1a (FOXO1a) on Ser322 and Ser325 within its MPD, without affecting the phosphorylation of other sites. It was also found that although the treatment of in HCT116 cells with D4476 led to a partial p53-dependent growth arrest, the induction of p53-independent apoptosis by D4476 suggested a critical role for the MDM2-CK1 complex in maintaining E2F-1 anti-apoptotic signaling.

References:

[1] Rena G, et al. D4476, a cell-permeant inhibitor of CK1, suppresses the site-specific phosphorylation and nuclear exclusion of FOXO1a. EMBO Rep. 2004 Jan;5(1):60-5.

[2] Huart AS, MacLaine NJ, Meek DW, Hupp TR. CK1α plays a central role in mediating MDM2 control of p53 and E2F-1 protein stability. J Biol Chem. 2009 Nov 20;284(47):32384-94.

Background

D4476 is a relatively specific and cell-permeant inhibitor of CK1 and ALK5 with respective IC₅₀ values of 0.3 and 0.5 µM at 0.1 mM ATP in vitro.[1]

CK1 (casein kinase 1) phosphorylates serine residues that are located close to another

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phosphoserine in multisite phosphorylation domains (MPDs). D4476 may be an ATP-competitive inhibitor of CK1. It weakly inhibits SAPK2a/p38 and does not inhibit PKB or SGK. In H4IIE cells, the site-specific phosphorylation (Ser322 and Ser325) of FOXO1a was inhibited at 50 and 125 μ M, which reduced the initial rate of nuclear exclusion[1]. In Hela cells, the phosphorylation(Ser185) of RhoB caused by CK1 was inhibited by D4476 at 50 μ M then the RhoB-dependent actin fiber formation was subsequently activated[2]. D4476 treatment has been observed to result in a partial p53-dependent growth arrest in HCT116 cells.[3]

References:

1. G. Rena, J. Bain, M. Elliott and P. Cohen, EMBO Rep 2004, 5, 60-65.
2. V. Tillement, I. Lajoie-Mazenc, A. Casanova, C. Froment, M. Penary, D. Tovar, R. Marquez, B. Monsarrat, G. Favre and A. Pradines, Exp Cell Res 2008, 314, 2811-2821.
3. A. S. Huart, N. J. MacLaine, D. W. Meek and T. R. Hupp, J Biol Chem 2009, 284, 32384-32394.

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