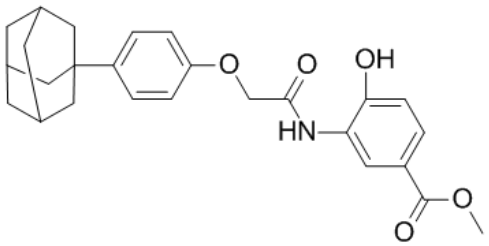
Product Data Sheet

Product Name: LW6 (HIF-1α inhibitor)
Cat. No.: GC32724

Chemical Properties

Cas. No.	934593-90-5		
SMILES	O=C(OC)C1=CC=C(O)C(NC(COC2=CC=C(C3(C4)CC5CC4CC(C5)C3)C=C2)=O)=C1		
Formula	$C_{26}H_{29}NO_5$	M.Wt	435.51
Solubility	DMSO : ≥ 33 mg/mL (75.77 mM)	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]:

Cell lines MDCKII-BCRP cells (overexpressing BCRP)

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Preparation Method	Cells were seeded into a 96-well plate. At 3 days post-seeding, cells were incubated with mitoxantrone (5μM) with/without inhibitor LW6 over the concentration range of 0.01-25μM. After incubation for 30 min, the drug solution was removed and the cells were washed twice with ice-cold PBS.
Reaction Conditions	0.01-25μM; 30 min
Applications	LW6 enhanced significantly the cellular accumulation of mitoxantrone(BCRP substrate).

Animal experiment [2]:

Animal models	Male ICR mice
Preparation Method	Mice were given a single intravenous (i.v.;5 mg/kg) or oral dose (p.o.;5 mg/kg) of LW6.
Dosage form	5 mg/kg;i.v/p.o;
Applications	LW6 exhibited a small volume of distribution (0.5 ±0.1 L/kg), and a short terminal half-life (0.6±0.1 h). LW6 was slowly degraded in mouse liver microsomes (t1/2 > 1 h) and serum (t1/2 > 6 h). About 54% or 44.8% of LW6 was available systemically as APA in the mouse after a single intravenous or oral administration, respectively.

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References:

[1]. Song JG, Lee YS, et,al.Discovery of LW6 as a new potent inhibitor of breast cancer resistance protein. Cancer Chemother Pharmacol. 2016 Oct;78(4):735-44. doi: 10.1007/s00280-016-3127-2. Epub 2016 Aug 12. PMID: 27520631.
[2].Lee JY, Lee K, et,al.Pharmacokinetic Characterization of LW6, a Novel Hypoxia-Inducible Factor-1α (HIF-1α) Inhibitor in Mice. Molecules. 2021 Apr 12;26(8):2226. doi: 10.3390/molecules26082226. PMID: 33921487; PMCID: PMC8070284.

Background

LW6 is a hypoxia-inducing factor 1(HIF) inhibitor, which effectively inhibits HIF-1α accumulation by degrading HIF-1α, but does not affect HIF-1A mRNA level during hypoxia. LW6 inhibits the expression of HIF and MDH2, with IC50 values of 4.4 and 6.3μM, respectively [1-2].

LW6(0.01-25μM ; 30 min) enhanced significantly the cellular accumulation of mitoxantrone(BCRP substrate)in MDCKII-BCRP cells (overexpressed BCRP)[3]. LW6 inhibited hypoxia-induced HIF1α expression at 20 mM in A549 cells, and at this concentration,LW6 induced hypoxia-selective apoptosis and decreased mitochondrial membrane potential[4]. LW6(40-160μM) inhibited proliferation and induced cell death in a dose-dependent manner In 6606PDA and MIA PaCa-2 cells[5]. LW6 (80μM)significantly inhibited migration,besides,LW6 reduced cell proliferation and induced cell death in a dose dependent manner[6]. LW6(30 μμ; 72 h) stimulates T cells to decrease HIF-1α levels[7]. LW6 inhibited T-cell clonal expansion in two-way mixed lymphocyte reaction (MLR) [8].

LW6(5 mg/kg;i.v/p.o) exhibited a small volume of distribution and a short terminal half-life. LW6 was slowly degraded in mouse liver microsomes and serum. About 54% or 44.8% of LW6 was available systemically as APA in the mouse after a single intravenous or oral administration, respectively[1].

References:
[1]. Lee K, Lee JH, et,al. (Aryloxyacetylamino)benzoic acid analogues: A new class of hypoxia-inducible factor-1 inhibitors. J Med Chem. 2007 Apr 5;50(7):1675-84. doi: 10.1021/jm0610292. Epub 2007 Mar 1. PMID: 17328532.
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hypoxia induced factor-1α/malate dehydrogenase 2 inhibitors. J Med Chem. 2014 Nov 26;57(22):9522-38. doi: 10.1021/jm501241g. Epub 2014 Nov 12. PMID: 25356789.
[3]. Song JG, Lee YS, et,al. Discovery of LW6 as a new potent inhibitor of breast cancer resistance protein. Cancer Chemother Pharmacol. 2016 Oct;78(4):735-44. doi: 10.1007/s00280-016-3127-2. Epub 2016 Aug 12. PMID: 27520631.
[4]. Sato M, Hirose K, et,al.LW6, a hypoxia-inducible factor 1 inhibitor, selectively induces apoptosis in hypoxic cells through depolarization of mitochondria in A549 human lung cancer cells. Mol Med Rep. 2015 Sep;12(3):3462-3468. doi: 10.3892/mmr.2015.3862. Epub 2015 May 27. PMID: 26017562; PMCID: PMC4526100.
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[7]. Eleftheriadis T, Pissas G, et,al. Malate dehydrogenase-2 inhibitor LW6 promotes metabolic adaptations and reduces proliferation and apoptosis in activated human T-cells. Exp Ther Med. 2015 Nov;10(5):1959-1966. doi: 10.3892/etm.2015.2763. Epub 2015 Sep 22. PMID: 26640580; PMCID: PMC4665222.
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