

Product Data Sheet

Product Name: JW 74
Cat. No.: GC13978

Chemical Properties

Cas. No. 863405-60-1

Chemical Name 4-[4-(4-methoxyphenyl)-5-[[[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl]thio]-4H-1,2,4-triazol-3-yl]-pyridine

SMILES CC(C=C1)=CC=C1C2=NOC(CSC3=NN=C(C4=CC=NC=C4)N3C5=CC=C(OC)C=C5)=N2

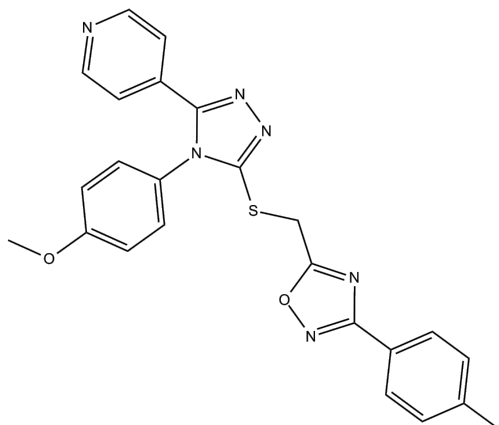
Formula $C_{24}H_{20}N_6O_2S$ M.Wt 456.5

Solubility $\leq 20\text{mg/ml}$ in DMSO; 20mg/ml in dimethyl formamide 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

Caution: Product has not been fully validated for medical applications. For research use only.

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Cell experiment: The cell lines U2OS, SaOS-2, and KPD are cultured in RPMI-1640. Two to three thousand cells attached overnight in 96-well plates are treated with culturing medium containing 0.1% DMSO (control) or JW74 (10-0.1 μ M). Proliferation rates based on cell confluence are determined by live cell imaging. Cellular viability is also determined by MTS assay. Expression of the proliferation marker Ki-67 is performed by staining cells with PE-mouse anti-human Ki-67 and by analyzing the expression by flow cytometry[2].

Animal experiment: Mice[1]40 female C.B-Igh-1b/IcrTac-Prkdcscid mice are injected subcutaneously (s.c.) at the right posterior flank with 107 SW480 cells diluted in 100 μ L PBS. Injections are initiated when tumor formation is visible in 50 % of the animals (7 days). Mice are randomized and divided into three treatment groups: JW74 150 mg/kg, JW74 300 mg/kg and vehicle control, 1 % Tween 80. Daily intra peritoneal (i.p.) injections (200 μ L) with two day injection intermissions after every fifth injection day are performed until the experiment end (29 days). At the termination day, 24 hours after the last injection, blood is collected after cardiac puncture and tumors are dissected and weighed. The compound concentration in tumors and blood are determined using on-line and off-line Solid Phase Extraction-Capillary Liquid Chromatography (SPE-CapLC) instrumentation coupled to a Time of Flight (TOF) mass spectrometer. A Zorbax SB C18 5 μ m 150 $\times$ 0.3 mm column is used for separation, and a Knauer K-2600 UV detector is used as a complimentary detector.

References:

- [1]. Waaler J, et al. Novel synthetic antagonists of canonical Wnt signaling inhibit colorectal cancer cell growth. Cancer Res. 2011 Jan 1;71(1):197-205.
[2]. Stratford EW, et al. The tankyrase-specific inhibitor JW74 affects cell cycle progression and induces apoptosis and differentiation in osteosarcoma cell lines. Cancer Med. 2014 Feb;3(1):36-46.

Background

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IC50: 790 nM for canonical Wnt signaling

JW 74 is an inhibitor of the catalytic PARP domain of TNKS1/2.

Wnt/ β -catenin, a major regulator of stem cell self-renewal and differentiation, is aberrantly activated in a several cancers, including osteosarcoma. Thus, attenuation of Wnt/ β -catenin activity by tankyrase inhibitors is an appealing strategy in osteosarcoma treatment.

In vitro: Previous study found that JW74 at the molecular level induced stabilization of AXIN2, a key component of the β -catenin destruction complex, leading to reduced levels of nuclear β -catenin. In addition, JW74 could induce reduced cell growth in all tested cell lines, partially due to a delay in cell cycle progression and partially because of an induction of caspase-3-mediated apoptosis. Moreover, JW74 was able to induce the differentiation in U2OS cells and also enhance differentiation of OS cell lines that did not harbor a differentiation block [1].

In vivo: Previous animal study found that the dose of 150 mg/kg of JW74 in ApcMin model could reduce the small intestinal adenoma by 48% and was comparable with celecoxib or rofecoxib. Furthermore, it was noteworthy that JW74 became rapidly cleared from the blood stream due to its poor in vivo stability [2].

Clinical trial: Up to now, JW 74 is still in the preclinical development stage.

References:

1. E. W. Stratford, J. Daffinrud, E. Munthe, et al. The tankyrase-specific inhibitor JW74 affects cell cycle progression and induces apoptosis and differentiation in osteosarcoma cell lines. Cancer Med. 3(1), 36-46 (2014).
2. Waaler J et al. Novel synthetic antagonists of canonical Wnt signaling inhibit colorectal cancer cell growth. Cancer Res. 2011 Jan 1;71(1):197-205.

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