Atuveciclib

Cat. No.: HY-12871B

Molecular Formula: $C_{18}H_{18}FN_5O_2S$

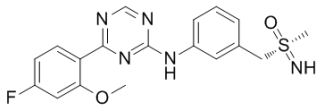
Molecular Weight: 387.43

Target: CDK

Pathway: Cell Cycle/DNA Damage

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 128.5 mg/mL (331.67 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5811 mL	12.9056 mL	25.8111 mL
5 mM	0.5162 mL	2.5811 mL	5.1622 mL
10 mM	0.2581 mL	1.2906 mL	2.5811 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

Atuveciclib (BAY-1143572) is a potent and highly selective, oral PTEFb/CDK9 inhibitor. Atuveciclib (BAY-1143572) inhibits CDK9/CycT1 with an IC_{50} of 13 nM[1].

IC_{50} & Target

CDK9/CycT1 13 nM (IC_{50})	CDK9/CycT1(h) 6 nM (IC_{50})	CDK3/CycE(h) 890 nM (IC_{50})	CDK2/CycE(h) 1000 nM (IC_{50})
CDK1/CycB(h) 1100 nM (IC_{50})	CDK5/p35(h) 1600 nM (IC_{50})		

In Vitro

Positive transcription elongation factor b (PTEFb) is a heterodimer of CDK9 and one of four cyclin partners, cyclin T1, cyclin K, cyclin T2a or cyclin T2b. Atuveciclib (BAY-1143572) demonstrates potent antiproliferative activity against HeLa cells (IC_{50} =920 nM) and MOLM-13 cells (IC_{50}=310 nM)[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

In vivo efficacy studies in the MOLM-13 xenograft model in mice, Atuveciclib (BAY-1143572) demonstrates great potency and

high antitumor efficacy. Daily administration of Atuveciclib (BAY-1143572) at 6.25 or 12.5 mg/kg results in a dose-dependent antitumor efficacy with a treatment-to-control (T/C) ratio of 0.64 and 0.49, respectively ($p<0.001$). In a separate experiment with a higher daily dose of 20 or 25 mg/kg Atuveciclib (BAY-1143572), antitumor efficacy with a T/C ratio of 0.41 and 0.31, respectively, is observed ($p<0.001$). The 25 mg/kg once daily dose is the maximum tolerated dose in nude mice. Furthermore, Atuveciclib (BAY-1143572) administered at 25 or 35 mg/kg, three days on / two days off, results in a T/C ratio of 0.33 and 0.20, respectively ($p<0.001$). Treatment with Atuveciclib (BAY-1143572) is well-tolerated, as demonstrated by less than 10 % mean body weight reduction throughout the study. In an in vivo pharmacokinetic study in rats, Atuveciclib (BAY-1143572) shows low blood clearance (CL_b 1.1 L/kg per hour)[1].

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PROTOCOL

Cell Assay [1]

HeLa human cervical tumor cells (CCL-2) and MOLM-13 human acute myeloid leukemia cells (ACC 554) are propagated under the suggested growth conditions in a humidified 37°C incubator. Proliferation assays are conducted in 96-well plates at densities of 3000 (HeLa) and 5000 (MOLM-13) cells per well in the growth medium containing 10 % fetal calf serum (FCS). Cells are treated in quadruplicate with serial dilutions of test compounds (e.g., Atuveciclib (BAY-1143572)) for 96 h. Relative cell numbers are quantified by crystal violet staining (HeLa) or CellTitre-Glo Luminescent Cell Viability Assay (MOLM-13). IC_{50} values are determined by means of a four-parameter fit on measurement data which are normalized to vehicle (DMSO) treated cells (=100 %) and measurement readings taken immediately before compound exposure (=0 %)[1].

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Animal Administration [1]

Mice and Rats[1]

For the acute myeloid leukemia (AML) mouse model, 2×10^6 MOLM-13 human AML cells are inoculated subcutaneously to the left flank of female NMRI nu/nu mice (18-21 g, 5-6 weeks). For the AML model in rats, 2×10^6 MV4-11 human AML cells are inoculated subcutaneously to the left flank of female athymic nude rats (160-200 g, 5-6 weeks). Animals are stratified into treatment and control groups (n=8-13/group for mice, n=12/group for rats) based on primary tumor size. Treatments are started 3-13 days after tumor cell inoculation when the average tumor sizes are 23-38 mm^2 and 43 mm^2 for mice and rats, respectively. The 20 and 25 mg/kg once daily dose is for nude mice. Furthermore, Atuveciclib (BAY-1143572) administered at 25 or 35 mg/kg, three days on/two days off. BAY-1143572 is administered daily oral administration of Atuveciclib (BAY-1143572) at 12 mg/kg for rats. Unless otherwise indicated, all treatments are administered orally (p.o.) and are continued until the end of the experiment. Body weight and tumor areas (longest diameter multiplied by its perpendicular) measured by caliper are determined at least twice weekly. T/C ratios are calculated by dividing the mean tumor area of the treatment group by the mean tumor area of the vehicle group at the time point when the vehicle group is sacrificed[1].

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CUSTOMER VALIDATION

- Cell Rep. 2020 Apr 7;31(1):107485.
- Cell Death Dis. 2020 Sep 15;11(9):754.
- Breast Cancer Res. 2019 Jul 1;21(1):77.
- Biomolecules. 2019 Sep 16;9(9):494.

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REFERENCES

[1]. Lücking U, et al. Identification of Atuveciclib (BAY 1143572), the First Highly Selective, Clinical PTEFb/CDK9 Inhibitor for the Treatment of Cancer. ChemMedChem. 2017

Nov 8;12(21):1776-1793.

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