Fadraciclib

Cat. No.: HY-101212

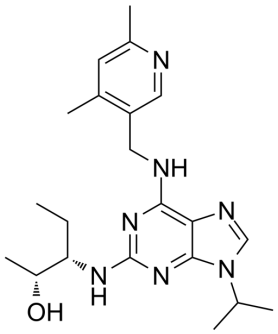
CAS No.: 1070790-89-4

Molecular Formula: $C_{21}H_{31}N_7O$

Molecular Weight: 397.52

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (251.56 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5156 mL	12.5780 mL	25.1560 mL
5 mM	0.5031 mL	2.5156 mL	5.0312 mL
10 mM	0.2516 mL	1.2578 mL	2.5156 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Fadraciclib (CYC065) is a second-generation, orally available ATP-competitive inhibitor of CDK2/CDK9 kinases[1] with IC_{50}s of 5 and 26 nM, respectively[2].

IC_{50} & Target

CDK2/CDK 9[1]

In Vitro

Fadraciclib blocks cells in the G1 phase of the cell cycle and inhibits cell growth specifically in cyclin E1 (CCNE1)-

	overexpressing uterine serous carcinomas (USCs). USC cell lines expressing high CCNE1 mRNA and protein levels to be significantly more sensitive to treatment with Fadraciclib in vitro when compared with low CCNE1-expressing cell lines (IC_{50}: mean±s.d.=124.1±57.8 nM in CCNE1-overexpressing USC cell lines vs 415±117.5 nM in CCNE1 low expressors, respectively; P=0.0003). Importantly, low concentrations of Fadraciclib (i.e., 100 nM) causes an arrest in the G1 phase of the cell cycle only in the CCNE1-overexpressing USC cell lines (i.e., USC-ARK-2, USC-ARK-7) [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	To evaluate the therapeutic potential of Fadraciclib as a single agent, USC-ARK-2-derived xenografts are treated daily with Fadraciclib (22.5 mg/kg) for a 3-week period. Tumor size and mouse weight are recorded two times a week. The daily administration of Fadraciclib results in a significant reduction of tumor growth compared with the vehicle-treated mice (P=0.012 starting at day 9 of the treatment). No significant weight loss is reported during the entire treatment period[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	The effect of CYC065 on the viability and IC_{50} of USC-ARK-1, USC-ARK-2, USC-ARK-7, USC-ARK-4 and USC-ARK-6 USC primary cell lines is determined in flow-cytometry assay. Briefly, tumour cells are plated in six-well plates and treated with a titration of CYC065 concentrations (i.e., ranging from 100 to 500 nM). After 72 h, cells are harvested, washed and stained with propidium iodide (PI; 5 µg/mL) for flow cytometric counts. The percentage of viable cells is then normalised considering the vehicle-treated cells as 100% viable. Half-maximal inhibitory concentration values are determined using GraphPad Prism5 version 6. For drug combination studies, USC-ARK-1 and USC-ARK-2 cell lines are incubated with the combination of Taselisib and CYC065 at multiple paired concentrations including the IC_{50}, the IC_{50}/2 and the IC_{50}*2 of each cell line to the corresponding drug (i.e., 10 nM of Taselisib and 198 nM of CYC065 for USC-ARK-1 and 50 nM of Taselisib and 62.5 nM of CYC065 for USC-ARK-2). Synergism is assessed by the combination index (CI). CI values <1 define a synergistic activity of the combination treatment. The CI values are calculated using the CompuSyn software[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] The in vivo efficacy of CYC065 used as a single agent is evaluated on xenograft mouse models derived from the CCNE1-amplified USC-ARK-2 USC cell line. Xenografts derived from the CCNE1-amplified, PIK3CA-mutated USC-ARK-1 cell line are used for evaluating the in vivo combination of CYC065 and Taselisib. Briefly, 5-7-week-old SCID mice are injected into the subcutaneous region with USC cells. A minimum of five animals per group are used. Treatments are administrated by oral gavage starting 1 week after tumor implantation when the size of the tumor is 0.125-0.150 cm^3. Uterine serous carcinoma-ARK-2-derived xenografts are divided into two groups: one group of animal receive the vehicle, whereas the experimental group receive CYC065 (22.5 mg/kg daily for 3 weeks). Uterine serous carcinoma-ARK-1-derived xenografts are instead divided into four groups: one group receive the vehicle (0.5% methylcellulose-0.2% Tween-80), one group receive CYC065 (22.5 mg/kg daily for 3 weeks), one group receive Taselisib (10 mg/kg daily, 5 days per week per 3 weeks) and the last group receive the combination of CYC065 and Taselisib. The size of the tumor at the initiation of treatment is 0.125-0.150 cm^3. Mouse weight and tumor size is recorded two times a week for the entire experimental period. Tumor volume is calculated. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2023 Jun 8;186(12):2628-2643.e21.
- Cell Death Dis. 2021 Aug 3;12(8):763.
- NPJ Precis Oncol. 2022 Sep 24;6(1):68.
- Cells. 2021 May 12;10(5):1182.
- Int J Mol Sci. 2022 Feb 24;23(5):2493.

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