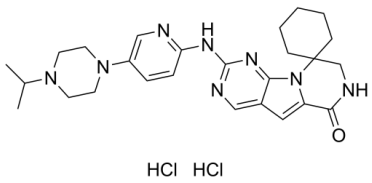
Data Sheet

Product Name:	Lerociclib (dihydrochloride)
Cat. No.:	CS-0063473
CAS No.:	2097938-59-3
Molecular Formula:	$C_{26}H_{36}Cl_2N_8O$
Molecular Weight:	547.52
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
Solubility:	H_2O : 5 mg/mL (ultrasonic;warming;heat to 60°C)



BIOLOGICAL ACTIVITY:

Lerociclib dihydrochloride (G1T38 dihydrochloride) is a potent and selective inhibitor of **CDK4**/**CDK6**, with **IC_{50}s** of 1 nM and 2 nM for **CDK4**/**CyclinD1** and **CDK6**/**CyclinD3**, respectively. ***In Vitro:*** Within the CDK family, Lerocyclib is least selective against CDK9/cyclin T, ~30 fold between CDK4/cyclin D1 and CDK9/ cyclin T at the biochemical IC_{50}. Lerociclib produces a robust and sustained G1 arrest in CDK4/6 dependent cells with an EC_{50} of ~20 nM. A dose dependent increase of cells in the G1 phase of the cell cycle is observed when CDK4/6 dependent WM2664 cells are treated with G1T38 for 24 hours. This arrest is maintained through 300 nM, more than 300x the biochemical IC_{50}. WM2664 cells treated with 30-1000 nM of Lerociclib for 24 hours exhibits a complete inhibition of RB phosphorylation compared to vehicle controls. Treatment with G1T38 reduces RB phosphorylation within 1 hour post-treatment and generates near complete inhibition of RB phosphorylation by 16 hours post-treatment. G1T38 produces a robust inhibition of proliferation in a diverse array of tumor cell lines including breast, melanoma, leukemia and lymphoma with EC_{50} concentrations as low as 23 nM[1]. ***In Vivo:*** In this $HER2^+$ breast cancer model, Mice treated with Lerociclib elicits 8% tumor regression after 21 days of treatment while control animals have a 577% increase in tumor burden over the same treatment period. Compared to the vehicle-treated mice, daily treatment with 100 mg/kg of Lerociclib or palbociclib shows tumor regression within 10 days in the MCF7 xenograft model. After 27 days of treatment, tumor growth inhibition is observed in the 10, 50, and 100 mg/kg Lerociclib cohorts (approximately 12%, 74%, and 90% inhibition, respectively). Daily oral palbociclib treatment causes an 18%, 66%, and 87% tumor growth inhibition in the 10, 50, and 100 mg/kg dosage cohorts, respectively. Interestingly, at 50 mg/kg, Lerociclib is significantly more efficaciou than palbociclib. Similar results are seen in the ER^+ ZR-75-1 breast cancer xenograft model when comparing Lerocyclib and palbociclib at the 50 mg/kg dose. Lerociclib treated mice exhibits 77% TGI with an overall 60% tumor growth delay demonstrating Lerociclib alone is highly efficacious in this NSCLC tumor model[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]**SupT1, Daudi, MCF7, ZR-75-1, A2058, WM2664, and H69 cells** are seeded at 1000 cells per well; **MV-4-11** and **BV173 cells** are plated at 4000 cells per well; **Tom-1 cells** are plated at 8,000 cells per well; **NALM-1 cells** are plated at 20,000 cells per well in Costar 3903 96 well plates. After 24 hours, plates are dosed with **Lerociclib** at a nine-point dose concentration from **10 μM to 1 nM**. Cell viability is determined after four or six days. Plates are processed on BioTek Synergy2 multi-mode plate reader and data analyzed using GraphPad Prism 5 statistical software[1].

Animal Administration: [1]Mice[1]

Female MMTV-NEU mice are used to test the efficacy of Lerociclib (100 mpk, medicated diet). At time of treatment, body composition is assessed and weight measurements (in grams) are recorded and used as a measure of gross toxicity. Female nude mice are implanted with NSCLC PDX CTG0159 tumor. Mice are then randomized into treatment groups and dosing initiated once

tumors reached a volume that fell within the range of 150-300 mm^3. **100 mg/kg Lerociclib** or vehicle is orally administered for 28 consecutive days. **Female NCI Ath/nu mice** are implanted with H1975 NSC lung adenocarcinoma model. Once tumors reach an average size of 100-150 mm^3, mice are randomized into treatment cohorts. Mice are orally administered daily Afatinib (20 mg/kg), Erlotinib (70 mg/kg), or **Lerociclib (50 or 100 mg/kg)**, as single agents or in combination (Lerociclib+Erlotinib or Lerociclib+Afatinib) for the duration of the study. All tumors are measured twice weekly until mice reach tumor burden of 1500 mm^3.

References:

[1]. Bisi JE, et al. Preclinical development of G1T38: A novel, potent and selective inhibitor of cyclin dependent kinases 4/6 for use as an oral antineoplastic in patients with CDK4/6 sensitive tumors. Oncotarget. 2017 Jun 27;8(26):42343-42358.

CAIndexNames:

Spiro[cyclohexane-1,9'(6'H)-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidin]-6'-one, 7',8'-dihydro-2'-[[5-[4-(1-methylethyl)-1-piperazinyl]-2-pyridinyl]amino]-, hydrochloride (1:2)

SMILES:

O=C1NCC2(N3C1=CC4=CN=C(NC5=NC=C(N6CCN(C(C)C)CC6)C=C5)N=C43)CCCCC2.Cl.Cl

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