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**Product Data Sheet**

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Product Name: ART812  
Cat. No.: GC64426

**Chemical Properties**

Cas. No. 2607138-82-7

Formula C<sub>19</sub>H<sub>16</sub>ClF<sub>4</sub>N<sub>3</sub>O<sub>4</sub> M.Wt 461.79

Solubility 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 HEK293 cells (human embryonic kidney cell line)

Preparation Method HEK293 cells were transfected with a NanoLuciferase-encoding TMEJ (Theta-Mediated End Joining) reporter substrate and a Firefly luciferase plasmid (for normalization). Cells were treated with ART812 (100–500nM) for 24 hours.

Reaction Conditions 100–500nM; 24 hours

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

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Applications	ART812 significantly inhibited TMEJ-mediated DNA repair in HEK293 cells, demonstrating a cellular EC <sub>50</sub> of 150nM.
<b>Animal experiment [2]:</b>	
Animal models	Female athymic nude mice (immunodeficient model)
Preparation Method	Mice were treated with either vehicle control or ART812 (150mg/kg; oral administration) for 4 days. Whole blood was collected on day 5 and fixed using a Mouse MicroFlow kit. Blood samples were analyzed for micronucleated reticulocytes (MN-RETs) by flow cytometry.
Dosage form	150mg/kg; oral administration
Applications	ART812 treatment demonstrated a 2-fold induction of micronuclei in reticulocytes, as measured by flow cytometry, indicating significant DNA damage and target engagement of Polθ.

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### References:

- [1] Zatreanu D, Robinson HMR, Alkhatib O, et al. Pol $\theta$  inhibitors elicit BRCA-gene synthetic lethality and target PARP inhibitor resistance. Nat Commun. 2021 Jun 17;12(1):3636.
- [2] Stockley ML, Ferdinand A, Benedetti G, et al. Discovery, Characterization, and Structure-Based Optimization of Small-Molecule In Vitro and In Vivo Probes for Human DNA Polymerase Theta. J Med Chem. 2022 Oct 27;65(20):13879-13891.

### Background

ART812 is an orally bioavailable small-molecule inhibitor of DNA polymerase theta (Pol $\theta$ ) with an IC<sub>50</sub> value of 7.6nM<sup>[1]</sup>. ART812 acts through an allosteric mechanism of inhibition, targeting the polymerase domain of Pol $\theta$ , thereby eliciting synthetic lethality in tumor cells deficient in homologous recombination (HR) repair<sup>[2]</sup>. ART812 has demonstrated single-agent anti-tumor efficacy in preclinical studies against models of PARP inhibitor-resistant cancer<sup>[3-4]</sup>.

In vitro, ART812 (100-500nM) treatment of HEK293 cells transfected with a microhomology-mediated end joining (MMEJ) reporter for 24 hours significantly inhibits TMEJ-mediated DNA repair activity<sup>[5]</sup>.

In vivo, ART812 (100mg/kg) administered orally once daily (QD) to female SRG OncoRats bearing established MDA-MB-436 BRCA1 mutant, SHLD2 knockout tumor xenografts significantly inhibited tumor growth and was well-tolerated over a 76-day treatment period<sup>[1]</sup>.

### References:

- [1] Zatreanu D, Robinson HMR, Alkhatib O, et al. Pol $\theta$  inhibitors elicit BRCA-gene synthetic lethality and target PARP inhibitor resistance. Nat Commun. 2021 Jun

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17;12(1):3636.

[2] Barszczewska-Pietraszek G, Drzewiecka M, Czarny P, et al. Polθ Inhibition: An Anticancer Therapy for HR-Deficient Tumours. *Int J Mol Sci.* 2022 Dec 24;24(1):319.

[3] Bazan Russo TD, Mujacic C, Di Giovanni E, et al. Polθ: emerging synthetic lethal partner in homologous recombination-deficient tumors. *Cancer Gene Ther.* 2024 Nov;31(11):1619-1631.

[4] Federica G, Michela C, Giovanna D. Targeting the DNA damage response in cancer. *MedComm (2020).* 2024 Oct 31;5(11):e788.

[5] Stockley ML, Ferdinand A, Benedetti G, et al. Discovery, Characterization, and Structure-Based Optimization of Small-Molecule In Vitro and In Vivo Probes for Human DNA Polymerase Theta. *J Med Chem.* 2022 Oct 27;65(20):13879-13891.

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