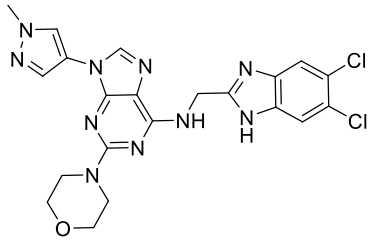
Product data sheet

MedKoo Cat#: 593163 Name: SR-4835 CAS#: 2387704-62-1 Chemical Formula: $C_{21}H_{20}Cl_2N_{10}O$ Exact Mass: 498.1199 Molecular Weight: 499.36	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
SR-4835 is a highly selective dual inhibitor of CDK12 and CDK13, which disables triple-negative breast cancer (TNBC) cells. Mechanistically, inhibition or loss of CDK12/CDK13 triggers intronic polyadenylation site cleavage that suppresses the expression of core DNA damage response proteins. This provokes a "BRCAness" phenotype that results in deficiencies in DNA damage repair, promoting synergy with DNA-damaging chemotherapy and PARP inhibitors.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	5.0	10.0

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.00 mL	10.01 mL	20.03 mL
5 mM	0.40 mL	2.00 mL	4.01 mL
10 mM	0.20 mL	1.00 mL	2.00 mL
50 mM	0.04 mL	0.20 mL	0.40 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Quereda V, Bayle S, Vena F, Frydman SM, Monastyrskyi A, Roush WR, Duckett DR. Therapeutic Targeting of CDK12/CDK13 in Triple-Negative Breast Cancer. Cancer Cell. 2019 Nov 11;36(5):545-558.e7. doi: 10.1016/j.ccell.2019.09.004. Epub 2019 Oct 24. PMID: 31668947.

2. Hopkins JL, Zou L. Induction of BRCAness in Triple-Negative Breast Cancer by a CDK12/13 Inhibitor Improves Chemotherapy. Cancer Cell. 2019 Nov 11;36(5):461-463. doi: 10.1016/j.ccell.2019.10.012. PMID: 31715127.

In vivo study

1. Quereda V, Bayle S, Vena F, Frydman SM, Monastyrskyi A, Roush WR, Duckett DR. Therapeutic Targeting of CDK12/CDK13 in Triple-Negative Breast Cancer. Cancer Cell. 2019 Nov 11;36(5):545-558.e7. doi: 10.1016/j.ccell.2019.09.004. Epub 2019 Oct 24. PMID: 31668947.

7. Bioactivity
Biological target:

Product data sheet

SR-4835 is a highly selective dual inhibitor of CDK12 and CDK13 with IC50 of 99 nM and Kd of 98 nM for CDK12 and IC50 of 4.9 nM for CDK13. SR-4835 disables triple-negative breast cancer (TNBC) cells.

In vitro activity

To assess the global effects of CDK12/CDK13 knockdown or inhibition on gene expression, RNA sequencing (RNA-seq) analyses were performed on cells treated with either SR-4835 or vehicle or following knockdown of CDK12 and/or CDK13 (Table S4). Ingenuity Pathway Analysis indicated that CDK12/CDK13 inhibition led to significant suppression of genes involved in DNA repair, DNA recombination, and cell-cycle checkpoint control, while significantly upregulated genes included those involved in S and G2-M progression and apoptosis. Furthermore, there was a high coincidence of differentially expressed pathways affected by pharmacologic and genetic silencing of CDK12 and CDK13 (Figures 4A–4E). For example, the ATM pathway was suppressed by both SR-4835 and dual CRISPR CDK12/CDK13 knockdown (Figures 4A–4E and S2A). Notably, only three pathways were significantly regulated by CDK13 knockdown (Figure 4C), whereas there was significant overlap of pathways affected by SR-4835 treatment and silencing of CDK12, or of CDK12 plus CDK13 (Figure 4E). Analyzing genes included in the ingenuity pathway analysis functions: “DNA damage response of cells, repair of DNA and formation of γ-H2AX” (Figure 4F; Table S5), revealed that almost 200 genes significantly regulated by SR-4835 ($p < 0.05$) were also altered in CDK12/CDK13 dual knockdown cells. Furthermore, the number of genes regulated by CDK12 knockdown, while smaller, were altered in the same direction as those affected by SR-4835 treatment. Both SR-4835 and dual CDK12/CDK13 knockdown regulated the expression of genes involved in DDR. Synthetic lethality in response to PARP inhibition has revealed a gene list, coined the BRCAness signature (Lord and Ashworth, 2016). Importantly, expression of BRCAness signature genes was downregulated in the cells treated with SR-4835 (Figure 4G). Indeed, 13 BRCAness genes were profoundly suppressed when compared with global changes provoked by SR-4835 treatment (Figure 4H; Table S6).

Reference: Cancer Cell. 2019 Nov 11;36(5):545-558.e7. https://linkinghub.elsevier.com/retrieve/pii/S1535-6108(19)30424-6

In vivo activity

To test the anti-tumor activity of SR-4835 an orthotopic, patient-derived xenograft (PDX) model (PDX4013) derived from a TNBC patient who had limited response to treatment with dasatinib and docetaxel was used. Based on pharmacokinetic analysis, it was determined that SR-4835 is orally bioavailable (Figure S7A). Once tumors reached 100 mm3, animals were randomized into four groups and the cohorts were administered vehicle or SR-4835. There was a marked decrease in tumor growth in mice treated with SR-4835 compared with vehicle-treated mice (Figures 6A and 6B). Endpoint studies determined that expression of DDR genes (both mRNA and protein) were reduced in tumors treated with SR-4835, whereas protein levels of γ-H2AX were elevated in all conditions compared with vehicle-treated mice (Figures 6C–6E). SR-4835 treatment alone did not provoke weight loss. Treatment with SR-4835 significantly impaired tumor growth and irinotecan was potent at reducing the tumor growth, where 20% of the mice showed complete tumor regression (2 out of 10; Figures 7A and 7B).

Reference: Cancer Cell. 2019 Nov 11;36(5):545-558.e7. https://linkinghub.elsevier.com/retrieve/pii/S1535-6108(19)30424-6

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.