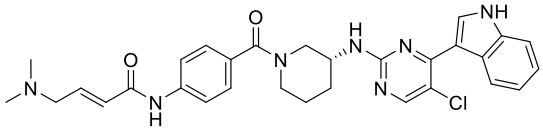
Product data sheet

MedKoo Cat#: 406959 Name: THZ531 CAS#: 1702809-17-3 Chemical Formula: $C_{30}H_{32}ClN_7O_2$ Exact Mass: 557.2306 Molecular Weight: 558.083	
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:

THZ531 is a covalent CDK12 and CDK13 covalent inhibitor. Cyclin-dependent kinases 12 and 13 (CDK12 and CDK13) play critical roles in the regulation of gene transcription. THZ531 irreversibly targets a cysteine located outside the kinase domain. THZ531 causes a loss of gene expression with concurrent loss of elongating and hyperphosphorylated RNA polymerase II. THZ531 substantially decreases the expression of DNA damage response genes and key super-enhancer-associated transcription factor genes. THZ531 dramatically induced apoptotic cell death. Small molecules capable of specifically targeting CDK12 and CDK13 may thus help identify cancer subtypes that are particularly dependent on their kinase activities.

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	17.15	30.73
DMF	30.0	53.76
Ethanol	25.0	44.80

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.79 mL	8.96 mL	17.92 mL
5 mM	0.36 mL	1.79 mL	3.58 mL
10 mM	0.18 mL	0.90 mL	1.79 mL
50 mM	0.04 mL	0.18 mL	0.36 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. Iniguez AB, Stolte B, Wang EJ, Conway AS, Alexe G, Dharia NV, Kwiatkowski N, Zhang T, Abraham BJ, Mora J, Kalev P, Leggett A, Chowdhury D, Benes CH, Young RA, Gray NS, Stegmaier K. EWS/FLI Confers Tumor Cell Synthetic Lethality to CDK12 Inhibition in Ewing Sarcoma. Cancer Cell. 2018 Feb 12;33(2):202-216.e6. doi: 10.1016/j.ccell.2017.12.009. Epub 2018 Jan 18. PMID: 29358035; PMCID: PMC5846483.
2. Zhang T, Kwiatkowski N, Olson CM, Dixon-Clarke SE, Abraham BJ, Greifenberg AK, Ficarro SB, Elkins JM, Liang Y, Hannett NM, Manz T, Hao M, Bartkowiak B, Greenleaf AL, Marto JA, Geyer M, Bullock AN, Young RA, Gray NS. Covalent targeting of remote cysteine residues to develop CDK12 and CDK13 inhibitors. Nat Chem Biol. 2016 Oct;12(10):876-84. doi: 10.1038/nchembio.2166. Epub 2016 Aug 29. PMID: 27571479; PMCID: PMC5033074.

In vivo study

Product data sheet

1. Iniguez AB, Stolte B, Wang EJ, Conway AS, Alexe G, Dharia NV, Kwiatkowski N, Zhang T, Abraham BJ, Mora J, Kalev P, Leggett A, Chowdhury D, Benes CH, Young RA, Gray NS, Stegmaier K. EWS/FLI Confers Tumor Cell Synthetic Lethality to CDK12 Inhibition in Ewing Sarcoma. Cancer Cell. 2018 Feb 12;33(2):202-216.e6. doi: 10.1016/j.ccell.2017.12.009. Epub 2018 Jan 18. PMID: 29358035; PMCID: PMC5846483.

7. Bioactivity

Biological target:

THZ531 is a covalent inhibitor of both CDK12 and CDK13 with IC50s of 158 nM and 69 nM, respectively.

In vitro activity

Coincident with THZ531 decreasing the elongating Pol II population, this study found that THZ531 downregulated the expression of certain genes in Jurkat T-ALL. At concentrations leading to complete CDK12 and 13 inhibition, genes encoding factors that regulate transcription were exceptionally sensitive to THZ531. At this concentration, the loss of expression of the most sensitive genes positively correlated with the amount of promoter and enhancer–bound CDK12 with super-enhancer—associated genes being especially sensitive. These data suggest that inhibition of CDK12, like that of CDK7, may provide another means of targeting super –enhancer –associated oncogene expression in various cancers. Additionally, this study found that genes involved in DDR were exquisitely sensitive to low doses of THZ531 and continue to lose expression with escalating doses of THZ531. A similar set of DDR genes was recently shown to be sensitive to loss of CDK12 and 13 cyclin K complexes. In contrast to THZ531 treatment, neither depletion of CDK12 and 13 nor mutations that disrupt complex integrity leads to gross disruption of the larger gene expression program. This discrepancy could be explained by numerous factors. This study favors the explanation that THZ531 treatment effectively creates an inactive or dominant negative CDK12 and 13 complexes, which elicits fundamentally different effects on transcription. However, the modest recovery of wild-type function following expression of CDK12 C1039S suggests that remaining CDK13 activity, or off-target activity on other transcription-associated kinases such as JNK1/2/3 (identified in Supplementary Table 1 and Data Set 2) or other unknown off-targets may also account for this discrepancy.

Reference: Nat Chem Biol. 2016 Oct; 12(10): 876–884. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5033074/

In vivo activity

Because THZ531 is not optimized for in vivo studies, this study used the parental compound, THZ1. Olaparib and THZ1 as single agents each significantly decreased tumor growth rate and extended the survival of the mice (median survival: 18 days in vehicle, 32 days in THZ1, and 28 days in the olaparib groups) (Figures 6A and 6B). A striking decreased tumor growth rate was observed when both drugs were used in combination (Figure 6A), and the combination treatment significantly extended survival compared with the vehicle control or either single agent (Figure 6B). Seventy percent of mice in the combination arm were still alive by day 40 when treatment was ended (Figure 6B).

Reference: Cancer Cell. 2018 Feb 12;33(2):202-216.e6. https://pubmed.ncbi.nlm.nih.gov/29358035/