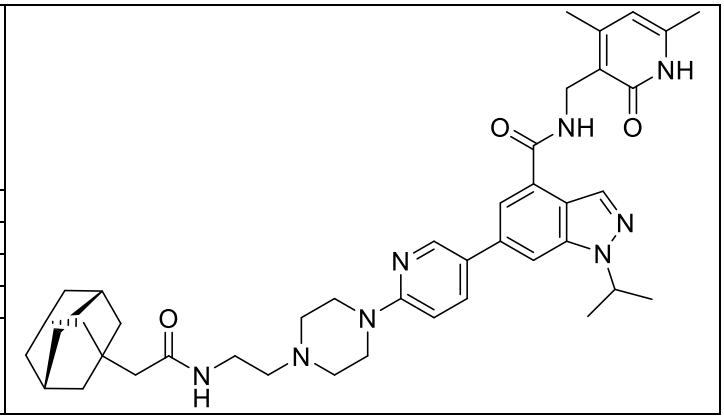
Product data sheet

MedKoo Cat#: 462549 Name: MS1943 CAS#: 2225938-17-8 Chemical Formula: $C_{42}H_{54}N_8O_3$ Exact Mass: 718.4319 Molecular Weight: 718.95	
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:
MS1943 is a first-in-class, orally bioavailable EZH2 selective degrader. It significantly reduces EZH2 protein levels in numerous triple-negative breast cancer (TNBC) and other cancer and noncancerous cell lines. MS1943 effectively blocks proliferation of multiple TNBC and other cancer cell lines.

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	100.0	139.1

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.39 mL	6.95 mL	13.91 mL
5 mM	0.28 mL	1.39 mL	2.78 mL
10 mM	0.14 mL	0.70 mL	1.39 mL
50 mM	0.03 mL	0.14 mL	0.28 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. Ma A, Stratikopoulos E, Park KS, Wei J, Martin TC, Yang X, Schwarz M, Leshchenko V, Rialdi A, Dale B, Lagana A, Guccione E, Parekh S, Parsons R, Jin J. Discovery of a first-in-class EZH2 selective degrader. Nat Chem Biol. 2020 Feb;16(2):214-222. doi: 10.1038/s41589-019-0421-4. Epub 2019 Dec 9. PMID: 31819273; PMCID: PMC6982609.

In vivo study

1. Ma A, Stratikopoulos E, Park KS, Wei J, Martin TC, Yang X, Schwarz M, Leshchenko V, Rialdi A, Dale B, Lagana A, Guccione E, Parekh S, Parsons R, Jin J. Discovery of a first-in-class EZH2 selective degrader. Nat Chem Biol. 2020 Feb;16(2):214-222. doi: 10.1038/s41589-019-0421-4. Epub 2019 Dec 9. PMID: 31819273; PMCID: PMC6982609.

7. Bioactivity
Biological target:

MS1943 is an EZH2 selective degrader with an IC50 value of 120 nM.

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In vitro activity

To gain mechanistic insights into how MS1943 induces cell death, MDA-MB-468 cells were treated with MS1943 or DMSO control and changes of gene expression were assessed using RNA-seq experiments. Interestingly, MS1943-treated cells were characterized by a unique set of deregulated genes that could readily separate them from control cells (Fig. 6a). It was identified that several PRC2 target gene programs, including Wnt/ß-catenin signaling (c-Myc, cyclin D1 and Axin2), RUNX3, CK5 and CK6, were significantly altered in MS1943-treated cells with a false discovery rate (FDR) at 5%, as when EZH2 is degraded. It was confirmed through quantitative real-time PCR that Xbp1 and its downstream effectors Chop and Bip were upregulated in response to treatment with MS1943 in MDA-MB-468 cells starting at 4 h of treatment and that induction was sustained for at least two days (Supplementary Fig. 14). Of note, the processed/spliced Xbp1 transcript (Xbp1–207) that can result in active XBP139 was the only transcript that was significantly upregulated after treatment with the degrader as evidenced by our RNA-seq data (Fig. 6c). Taken together, these data suggest that EZH2 degradation could result in sustained overactivation of the UPR pathway in MS1943-sensitive cells due to prolonged ER stress, which in turn could be deleterious and lead to apoptosis. To test this hypothesis, MDA-MB-468 cells (which are sensitive to MS1943) and MDA-MB-231 cells (which are insensitive to MS1943) were treated with the ER-stress inducer tunicamycin and found that it effectively induced cell death in MDA-MB-468 cells but not in MDA-MB-231 cells (Fig. 6d and Supplementary Fig. 15). These results suggest hat MS1943 mediates its cytotoxic effects through ER stress and UPR induction in cells that are dependent for their growth on EZH2.

Nat Chem Biol. 2020 Feb; 16(2): 214–222. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6982609/

In vivo activity

It was decided to evaluate the in vivo antitumor activity of MS1943 by treating mice bearing MDA-MB-468 tumor xenografts with 150 mg per kg body weight once daily i.p. injection of MS1943. Importantly, tumor growth was completely suppressed by MS1943, in comparison to the vehicle group (Fig. 4b). At this dose, MS1943 was well tolerated by the test mice, which did not exhibit any weight loss or other overt toxicities (Fig. 4c). To further investigate the effects of MS1943 in vivo, tumor samples were analyzed at the endpoint of the experiment using immunohistochemistry. Consistent with the in vitro data, a significant reduction of both EZH2 protein levels and H3K27me3 mark were observed in the tumors from mice treated with MS1943 (Fig. 5a,b). The antitumoral effect of MS1943 was due to increased apoptosis, as measured by cleaved caspase-3 levels, as well as decreased proliferation, as measured by staining with Ki-67 (Fig. 5a,b). Thus, a PK/PD relationship has been established for MS1943 in this tumor xenograft model. Overall, MS1943 was efficacious in vivo and well tolerated in mice at the efficacious dose.

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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.