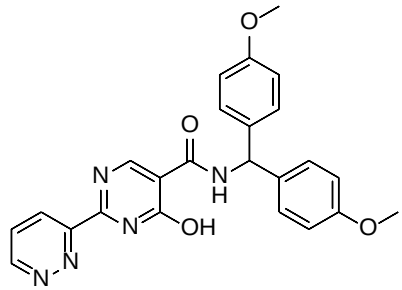
Product data sheet

MedKoo Cat#: 530342 Name: MK-8617 CAS#: 1187990-87-9 Chemical Formula: $C_{24}H_{21}N_5O_4$ Exact Mass: 443.1594 Molecular Weight: 443.46	
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:
MK-8617 is a potent, selective, orally bioavailabl Pan-Inhibitor of Hypoxia-Inducible Factor Prolyl Hydroxylase 1−3 (HIF PHD1−3) for the Treatment of Anemia (PHD2 IC50 = 1.0 nM; 10-19 hr dog and moneky t1/2). Anemia is a condition of insufficient red blood cells (RBCs) or hemoglobin (Hb) levels that result in reduced functional capability, fatigue, and shortness of breath.

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	5.67	12.79
DMSO:PBS (pH 7.2) (1:3)	0.25	0.56
DMF	1.0	2.25

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.25 mL	11.27 mL	22.55 mL
5 mM	0.45 mL	2.25 mL	4.51 mL
10 mM	0.23 mL	1.13 mL	2.25 mL
50 mM	0.05 mL	0.23 mL	0.45 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. Li ZL, Lv LL, Wang B, Tang TT, Feng Y, Cao JY, Jiang LQ, Sun YB, Liu H, Zhang XL, Ma KL, Tang RN, Liu BC. The profibrotic effects of MK-8617 on tubulointerstitial fibrosis mediated by the KLF5 regulating pathway. FASEB J. 2019 Nov;33(11):12630-12643. doi: 10.1096/fj.201901087RR. Epub 2019 Aug 26. PMID: 31451021; PMCID: PMC6902673.

In vivo study

1. Qian FY, Li ZL, Guo YD, Gao HC, Gu LH, Le K, Xie CM, Wang B, Zhang ZJ. Hypoxia-inducible factor-prolyl hydroxylase inhibitor ameliorates myopathy in a mouse model of chronic kidney disease. Am J Physiol Renal Physiol. 2019 Nov 1;317(5):F1265-F1273. doi: 10.1152/ajprenal.00260.2019. Epub 2019 Oct 7. PMID: 31588798.

7. Bioactivity
Biological target: MK-8617 is a pan-inhibitor of hypoxia-inducible factor prolyl hydroxylase 1-3 (HIF PHD1-3) with an IC50 of 1 nM for PHD2.

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In vitro activity

To investigate the exact mechanisms of the fibrogenic effect induced by MK-8617 (MK), a genome-wide gene expression analysis was performed in MK-stimulated HK-2 cells at low (50 nM) and high (1000 nM) doses. KLF5 expression appeared to be markedly up-regulated in high-dose MK-stimulated HK-2 cells (Fig. 5A). After 1000 nM MK administration in vitro, KLF5 mRNA and protein expression were significantly up-regulated (Supplemental Fig. S5E, F). These data indicate that KLF5 might be involved in TIF induction by high-dose MK. To determine the exact mechanisms of KLF5 up-regulation induced by MK, in silico analysis was employed. Computational transcription factor-binding site prediction in the promoter region suggested that HIF-1α may transcriptionally regulate KLF5 (Supplemental Fig. S6). HIF-1α did not bind to the KLF5 promoter under basal conditions and low-dose (50 nM) MK treatment, but HIF-1α binding could be enriched on this promoter by high-dose (1000 nM) MK administration to HK-2 cells (Fig. 5D), demonstrating the direct interaction between HIF-1α and KLF5 in response to high-dose MK. HIF-1α is therefore a strong positive regulator of the KLF5 gene during high-dose MK treatment.

Reference: FASEB J. 2019 Nov;33(11):12630-12643. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902673/

In vivo activity

Whether pharmacological activation of HIF by MK-8617 (MK) improves CKD (chronic kidney disease) associated myopathy was assessed in vivo. Mice were divided into sham or CKD groups, and CKD mice were subdivided into CKD + vehicle or MK treatment groups (1.5, 5, or 12.5 mg/kg for 12 wk). In CKD mice, skeletal muscle mass, mitochondrial amount, and exercise capacity decreased compared with sham mice. Compared with the CKD + vehicle group, low (1.5 mg/kg) and medium (5 mg/kg) doses of MK, but not the high dose (12.5 mg/kg), significantly restored these changes and was accompanied by incremental increases in HIF-1α. Furthermore, increased capillary density and area were observed in a MK dose-dependent manner, which is likely related to an improved VEGF response in the skeletal muscle of CKD mice. In addition, macrophage and proinflammatory cytokines, including monocyte chemoattractant protein 1, TNF-α, and IL-6, significantly increased in the high-dose MK group.

Reference: Am J Physiol Renal Physiol. 2019 Nov 1;317(5):F1265-F1273.
https://journals.physiology.org/doi/full/10.1152/ajprenal.00260.2019?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org

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.