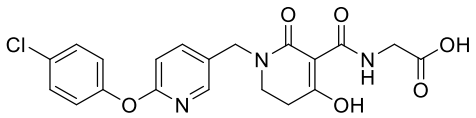
Product data sheet

MedKoo Cat#: 555388 Name: TP0463518 CAS#: 1558021-37-6 Chemical Formula: $C_{20}H_{18}ClN_3O_6$ Exact Mass: 431.0884 Molecular Weight: 431.829	
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:
TP0463518 is a novel, highly potent HIF prolyl hydroxylase (PHD) inhibitor. TP0463518 competitively inhibited human PHD2 with a Ki value of 5.3 nM. TP0463518 also inhibited human PHD1/3 with IC50 values of 18 and 63 nM as well as monkey PHD2 with an IC50 value of 22 nM. In normal mice and rats, TP0463518 significantly increased the serum EPO levels at doses of 5 and 20 mg/kg, respectively.

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	40	92.63

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.32 mL	11.58 mL	23.16 mL
5 mM	0.46 mL	2.32 mL	4.63 mL
10 mM	0.23 mL	1.16 mL	2.32 mL
50 mM	0.05 mL	0.23 mL	0.46 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. Kato S, Ochiai N, Takano H, Io F, Takayama N, Koretsune H, Kunioka EI, Uchida S, Yamamoto K. TP0463518, a Novel Prolyl Hydroxylase Inhibitor, Specifically Induces Erythropoietin Production in the Liver. J Pharmacol Exp Ther. 2019 Dec;371(3):675-683. doi: 10.1124/jpet.119.258731. Epub 2019 Oct 4. PMID: 31585986.

In vivo study

1. Kato S, Takayama N, Takano H, Koretsune H, Koizumi C, Kunioka EI, Uchida S, Takahashi T, Yamamoto K. TP0463518, a novel inhibitor for hypoxia-inducible factor prolyl hydroxylases, increases erythropoietin in rodents and monkeys with a good pharmacokinetics-pharmacodynamics correlation. Eur J Pharmacol. 2018 Nov 5;838:138-144. doi: 10.1016/j.ejphar.2018.08.044. Epub 2018 Sep 1. PMID: 30179610.

2. Kato S, Ochiai N, Takano H, Io F, Takayama N, Koretsune H, Kunioka EI, Uchida S, Yamamoto K. TP0463518, a Novel Prolyl Hydroxylase Inhibitor, Specifically Induces Erythropoietin Production in the Liver. J Pharmacol Exp Ther. 2019 Dec;371(3):675-683. doi: 10.1124/jpet.119.258731. Epub 2019 Oct 4. PMID: 31585986.

7. Bioactivity

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Biological target:

TP0463518 is a potent hypoxia-inducible factor prolyl hydroxylases (PHDs) inhibitor with a Ki value of 5.3 nM for human PHD2.

In vitro activity

To examine whether TP0463518 exerts EPO-producing effect in the liver cells, we addressed the effect of TP0463518 on EPO mRNA expression and EPO secretion in the human and rat liver cell lines, HepG2 and H4-II-E-C3. After the treatment of the cells with TP0463518 for 24 hours, EPO mRNA levels in both HepG2 and H4-II-E-C3 cells increased at 10 μM or more; the increase at 30 μM was 4.04- and 3.47-fold higher than control group, respectively (Fig. 8, A and B). EPO concentration in the medium of HepG2 cells treated with TP0463518 for 72 hours increased from 38.7 mU/ml in control wells to 74.0 mU/ml at 30 μM (Fig. 8C). EPO concentration in medium of H4-II-E-C3 cells treated with TP0463518 for 72 hours also increased from 79.1 pg/ml in control wells to 254.9 pg/ml at 30 μM (Fig. 8D). These results indicated that TP0463518 increased EPO expression not only in rat liver but also in human liver.

Reference: J Pharmacol Exp Ther. 2019 Dec;371(3):675-683.
https://jpet.aspetjournals.org/cgi/pmidlookup?view=long&pmid=31585986

In vivo activity

The effect of TP0463518 in inducing EPO production in the kidney and liver was examined by measuring the hypoxia-inducible factor 2α (HIF-2α), EPO mRNA, and serum EPO levels in normal and bilaterally nephrectomized rats. Furthermore, whether liver-derived EPO improved anemia was investigated in 5/6 nephrectomized (5/6 Nx) rats. TP0463518 scarcely increased the HIF-2α and EPO mRNA expression levels in the kidney cortex, whereas oral administration of TP0463518 at 40 mg/kg dramatically increased the HIF-2α level from 0.27 to 1.53 fmol/mg and the EPO mRNA expression level by 1300-fold in the livers of healthy rats. After administration of TP0463518 at 20 mg/kg, the total EPO mRNA expression level in the whole liver was 22-fold that in the whole kidney. In bilaterally nephrectomized rats, TP0463518 raised the serum EPO concentration from 0 to 180 pg/ml at 20 mg/kg. Furthermore, repeated administration of TP0463518 at 10 mg/kg increased the reticulocyte count in 5/6 Nx rats on day 7 and raised the hemoglobin level on day 14. The present study revealed that TP0463518 specifically induced EPO production in the liver and improved anemia. The characteristic feature of TP0463518 would lead to not only a more detailed understanding of the PHD-HIF2α-EPO pathway in erythropoiesis, but a new therapeutic alternative for renal anemia.

Reference: J Pharmacol Exp Ther. 2019 Dec;371(3):675-683.
https://jpet.aspetjournals.org/cgi/pmidlookup?view=long&pmid=31585986