

## Product Data Sheet

Product Name: MGL-3196

Cat. No.: GC18243

### Chemical Properties

Cas. No. 920509-32-6

Chemical Name 2-[3,5-dichloro-4-[[1,6-dihydro-5-(1-methylethyl)-6-oxo-3-pyridazinyl]oxy]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile

SMILES O=C(N1)N(C2=CC(Cl)=C(OC3=NNC(C(C(C)C)=C3)=O)C(Cl)=C2)N=C(C#N)C1=O

Formula  $C_{17}H_{12}Cl_2N_6O_4$

M.Wt 435.2

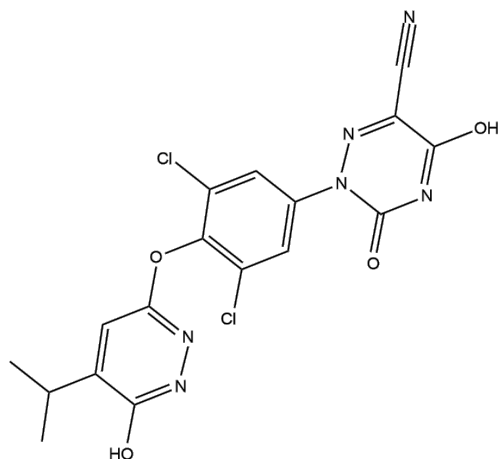
Solubility DMF: 20 mg/ml, DMSO: 20 mg/ml, Ethanol: 1 mg/ml

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



### Protocol

#### Cell experiment [1]:

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Cell lines                      HEK-1B1 cells

HEK-1B1 cells were maintained in a DMEM containing 4.5g/L glucose, 1% pyruvate (DMEM+GlutaMAX), 1% ZellShield, and 10% FCS supplemented with 800µg/mL G418. Only those cells in a passage number below 7 were used for the experiments. MGL-3196 were dissolved in DMSO at a concentration of

Preparation Method 10mM.  $8 \times 10^5$  HEK-1B1 cells were seeded in a 6-well dish and grown to 60-80% confluence overnight. After 24h in the TH-depleted medium, HEK-1B1 cells were treated with MGL-3196 (6µM) or DMSO (control) for another 48h. The total RNA was extracted for gene expression analysis. The oxygen consumption rate (OCR) was measured with an XF24 extracellular analyzer.

Reaction  
Conditions                      6µM; 48h

Applications                      Treatment of HEK-1B1 cells with MGL-3196 significantly induced the expression of THRβ target genes like KLF9 and PCK1 and enhanced mitochondrial respiration.

### Animal experiment [2]:

Animal models                      C57BL/6 SPF mice

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C57BL/6 SPF mice (6-week-old) were housed in rigid autoclaved cages (6 per cage) under a 12-h light-dark cycle. All mice were firstly fed with a MASH diet containing 21.1% kcal fat, 1.25% kcal cholesterol and 41.0% kcal sucrose by a sugar water solution of 23.1g/L d-fructose and 18.9g/L d-glucose for 16 weeks to induce MASH. For in vivo experiments, each group of the above MASH mice were directly gavaged with 3mg/kg MGL-3196 (daily, the same volume of saline as the solvent control) for 8 weeks. Their body weights and food intake were monitored weekly. Their fecal samples were collected for metagenomic and metabonomic analysis. Ultimately, all mice were euthanized by exsanguination to collect their colonic, serum and hepatic samples to determine serological, standard H&E, Sirius red staining and Oil red O histological analysis, respectively.

### Preparation Method

Dosage form      3mg/kg/day; gavage; 8 weeks

Applications      MGL-3196 reduced liver weight, circulating triglycerides and total cholesterol, and improved histological signs of steatosis and fibrosis in SPF mice fed a MASH diet.

### References:

- [1] Hones GS, Sivakumar RG, Hoppe C, König J, Führer D, Moeller LC. Cell-Specific Transport and Thyroid Hormone Receptor Isoform Selectivity Account for Hepatocyte-Targeted Thyromimetic Action of MGL-3196. *Int J Mol Sci.* 2022;23(22):13714.
- [2] Zhang YH, Xie R, Dai CS, et al. Thyroid hormone receptor-beta agonist HSK31679 alleviates MASLD by modulating gut microbial sphingolipids. *J Hepatol.* 2025;82(2):189-202.

### Background

MGL-3196 is a highly selective and orally active thyroid hormone receptor  $\beta$  (THR $\beta$ ) agonist with an EC<sub>50</sub> value of 0.21 $\mu$ M<sup>[1]</sup>. THR $\beta$  is a nuclear receptor that plays a key role in regulating metabolism, growth, and development by binding to thyroid hormones and modulating gene expression<sup>[2]</sup>. MGL-

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3196 can be used for the study of nonalcoholic steatohepatitis and cardiovascular diseases<sup>[3][4]</sup>.

In vitro, treatment of HEK-1B1 cells with MGL-3196 (6 $\mu$ M; 48h) significantly induced the expression of THR $\beta$  target genes like KLF9 and PCK1 and enhanced mitochondrial respiration<sup>[5]</sup>.

In vivo, MGL-3196 (3mg/kg/day; gavage; 8 weeks) reduced liver weight, circulating triglycerides and total cholesterol, and improved histological signs of steatosis and fibrosis in SPF mice fed a MASH diet<sup>[6]</sup>. MGL-3196 (1mg/kg/day; orally; 8 weeks) significantly reduced liver weight, improved histological steatosis and lobular inflammation scores, and lowered plasma cholesterol and alanine transaminase (ALT) levels in a mouse model of fatty liver disease induced by the GAN diet<sup>[7]</sup>.

### References:

- [1] Kelly MJ, Pietranico-Cole S, Larigan JD, et al. Discovery of 2-[3,5-dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile (MGL-3196), a Highly Selective Thyroid Hormone Receptor  $\beta$  agonist in clinical trials for the treatment of dyslipidemia. *J Med Chem.* 2014;57(10):3912-3923.
- [2] Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev.* 2014;94(2):355-382.
- [3] Keam SJ. Resmetirom: First Approval. *Drugs.* 2024;84(6):729-735.
- [4] Zisis M, Chondrogianni ME, Androutsakos T, et al. Linking Cardiovascular Disease and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): The Role of Cardiometabolic Drugs in MASLD Treatment. *Biomolecules.* 2025;15(3):324.
- [5] Hones GS, Sivakumar RG, Hoppe C, König J, Führer D, Moeller LC. Cell-Specific Transport and Thyroid Hormone Receptor Isoform Selectivity Account for Hepatocyte-Targeted Thyromimetic Action of MGL-3196. *Int J Mol Sci.* 2022;23(22):13714.
- [6] Zhang YH, Xie R, Dai CS, et al. Thyroid hormone receptor-beta agonist HSK31679 alleviates MASLD by modulating gut microbial sphingolipids. *J Hepatol.* 2025;82(2):189-202.
- [7] Zhou M, Li C, Byrne FL, et al. Beneficial effects of MGL-3196 and BAM15 combination in a mouse model of fatty liver disease. *Acta Physiol (Oxf).* 2024;240(10):e14217.

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