Trimetrexate

Cat. No.: HY-10373

CAS No.: 52128-35-5

Molecular Formula: $C_{19}H_{23}N_5O_3$

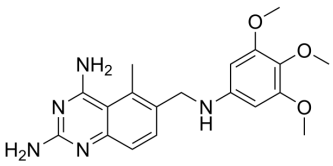
Molecular Weight: 369.42

Target: Bacterial; Antibiotic; Antifolate; Parasite; DNA/RNA Synthesis; Dihydrofolate reductase (DHFR)

Pathway: Anti-infection; Cell Cycle/DNA Damage; Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 61.5 mg/mL (166.48 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent, Mass	1 mg	5 mg	10 mg
1 mM	2.7069 mL	13.5347 mL	27.0695 mL
5 mM	0.5414 mL	2.7069 mL	5.4139 mL
10 mM	0.2707 mL	1.3535 mL	2.7069 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 40 mg/mL (108.28 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.77 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.77 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Trimetrexate (CI-898) is an antibiotic, also a potent and orally active dihydrofolate reductase (DHFR) inhibitor, reducing the production of DNA and RNA precursors and leading to cell death, with IC_{50} values of 4.74 nM and 1.35 nM for human DHFR and Toxoplasma gondii DHFR. Trimetrexate can also inhibit the growth of various cancer cells. Trimetrexate can be used for researching Pneumocystis carinii pneumonia (PCP) and cancer[1][2][3][4][5].

IC_{50} & Target	Toxoplasma

In Vitro

Trimetrexate (0.1 μM, 18 h) completely inhibits proliferation of toxoplasma in murine macrophages[3].
Trimetrexate (1 μM) can cross the toxoplasma cell membrane and rapidly reaches high intracellular concentrations (108 pmol/10^7 cells within 10 min) [3].
Trimetrexate (0.1 mM; 24 h) inhibits cell growth by 50-60% in SNU-C4 and NCI-H630 cell lines[5].
Trimetrexate (1 and 10 mM; 24 h) produces lethality and inhibits DHFR in C4 cells[5].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[5]

Cell Line:	SNU-C4 and NCI-H630
Concentration:	0.1 mM
Incubation Time:	24 h
Result:	Inhibited cell growth by 50-60% in both cell lines.

Cell Proliferation Assay[5]

Cell Line:	C4 cells
Concentration:	1 and 10 mM
Incubation Time:	24 h
Result:	Produced 42% and 50% lethality at 1 and 10 mM, respectively.

In Vivo

Trimetrexate (180 mg/kg or 30 mg/kg; p.o. or i.p.; daily) extends the median survival of the toxoplasma infected mice and shows antitoxoplasma activity[3]. Trimetrexate (0-30 mg/kg; i.v.; once daily for 5days) shows chronic toxicity in rats[4].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Toxoplasma infected female BALB/c mice weighing about 20 g[3]
Dosage:	180 mg/kg or 30 mg/kg
Administration:	180 mg/kg per day orally in the drinking water or 30 mg/kg per day i.p.
Result:	Extended the median survival of the infected mice to 10 d (p.o.) or 19 d (i.p.).

Animal Model:	Charles River Wistar Crl(WI)BR rats weighing approximately 150 to 200 g[4]
Dosage:	0, 1, 10, or 30 mg/kg
Administration:	Intravenous injection, once daily for 5 consecutive days followed by a 23-day recovery period
Result:	Showed chronic toxicity, the testicular changes persisting during the course of multiple cycles of dosing were not reversible within 21 days, but required an additional 56 days for essentially complete recovery.

REFERENCES

[1]. Fulton, B., et al. Trimetrexate. Drugs 49, 563–576 (1995).

[2]. Hopper AT, et al. Discovery of Selective Toxoplasma gondii Dihydrofolate Reductase Inhibitors for the Treatment of Toxoplasmosis. J Med Chem. 2019 Feb 14;62(3):1562-1576.

[3]. Allegra CJ, et al. Potent in vitro and in vivo antitoxoplasma activity of the lipid-soluble antifolate trimetrexate. J Clin Invest. 1987 Feb;79(2):478-82.

[4]. Dethloff LA, et al. Chronic toxicity of the anticancer agent trimetrexate in rats. Fundam Appl Toxicol. 1992 Jul;19(1):6-14.

[5]. Grem JL, Voeller DM, Geoffroy F, Horak E, Johnston PG, Allegra CJ. Determinants of trimetrexate lethality in human colon cancer cells. Br J Cancer. 1994 Dec;70(6):1075-84.

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