Proguanil

Cat. No.: HY-B0806

CAS No.: 500-92-5

Molecular Formula: $C_{11}H_{16}ClN_5$

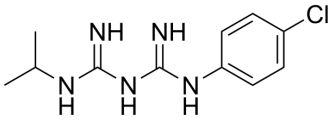
Molecular Weight: 253.73

Target: Parasite; Antifolate

Pathway: Anti-infection; Cell Cycle/DNA Damage

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 : ≥ 130 mg/mL (512.36 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.9412 mL	19.7060 mL	39.4120 mL
5 mM	0.7882 mL	3.9412 mL	7.8824 mL
10 mM	0.3941 mL	1.9706 mL	3.9412 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.17 mg/mL (8.55 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.17 mg/mL (8.55 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.17 mg/mL (8.55 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Proguanil, an antimalarial proagent, is metabolized to the active metabolite Cycloguanil (HY-12784). Proguanil is a dihydrofolate reductase (DHFR) inhibitor[1][2].

IC_{50} & Target

Plasmodium

In Vitro

Proguanil per se has only weak antimalarial activity in vitro (IC_{50}=2.4-19 μM), and its effectiveness depends on the active

	metabolite Cycloguanil (IC_{50}=0.5-2.5 nM). The Cycloguanil is a dihydrofolate reductase (DHFR) inhibitor. The combination of Atovaquone and Proguanil is synergistic in vitro. Both drugs also have activity against gametocytes and pre-erythrocytic (hepatic) stages of malaria parasites[1]. Proguanil acts as a biguanide rather than as its metabolite Cycloguanil (a parasite dihydrofolate reductase [DHFR] inhibitor) to enhance the Atovaquone effect. Proguanil-mediated enhancement is specific for Atovaquone, since the effects of other mitochondrial electron transport inhibitors, such as Myxothiazole and Antimycin, are not altered by inclusion of Proguanil[2]. $5\text{-}HT_3$ receptor responses are reversibly inhibited by Proguanil, the metabolite 4-chlorophenyl-1-biguanide (CPB) and the active metabolite Cycloguanil (CG), with an IC_{50} of 1.81, 1.48 and 4.36 μM, respectively[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Proguanil (p.o.; 2.9 mg/kg body weight; daily for 5 days and 6 weeks respectively) shows mild degenerative changes for five days, while shows severe degenerative changes for six weeks in wistar strain albino rats[4]. Serum testosterone level is significantly decreased for proguanil treatment rats[4]. Administration of Malarone (atovaquone and proguanil) to experimentally B. gibsoni infected two dogs in chronic stage and three dogs in acute stage results in decrease in parasitemia, and clinical improvements are observed[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [4]	Sertoli cells obtained from sixteen to eighteen day-old-rats are cultured and treated with 0.3 μM to 10 μM of proguanil for 5 days after which Sertoli cell viability and nuclei integrity are determined. Also, the genetic expressions of transferrin and Glial cell line-derived neurotrophic factor are assessed[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [4]	Rats: Groups of ten to twelve-week-old rats are administered proguanil (2.9 mg/kg body weight) daily for 5 days and 6 weeks respectively. Thereafter, body and reproductive organ weights are taken, sperm parameters are analyzed, while the histology of the testis and epididymis are carried out. Also, serum levels of testosterone, luteinizing hormone and follicle stimulating hormone are determined[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Pudney M, et al. Atovaquone and proguanil hydrochloride: a review of nonclinical studies. J Travel Med. 1999 May;6 Suppl 1:S8-12.

[2]. Srivastava IK, et al. A mechanism for the synergistic antimalarial action of atovaquone and proguanil. Antimicrob Agents Chemother. 1999 Jun;43(6):1334-9.

[3]. Lochner M, et al. The antimalarial drug proguanil is an antagonist at 5-HT3 receptors. J Pharmacol Exp Ther. 2014 Dec;351(3):674-84.

[4]. Stephen AO, et al. Prolonged administration of proguanil induces reproductive toxicity in male rats. J Toxicol Sci. 2011 Oct;36(5):587-99.

[5]. Iguchi A, et al. The in vitro interactions and in vivo efficacy of atovaquone and proguanil against Babesia gibsoni infection in dogs. Vet Parasitol. 2013 Nov 8;197(3-4):527-33.

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