Product Data Sheet

Product Name: DDD107498
Cat. No.: GC17285

Chemical Properties

Cas. No.	1469439-69-7		
Chemical Name	6-fluoro-2-(4-(morpholinomethyl)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide		
SMILES	O=C(NCCN1CCCC1)C2=CC(C3=CC=C(CN4CCOCC4)C=C3)=NC5=CC=C(F)C=C52		
Formula	$C_{27}H_{31}FN_4O_2$	M.Wt	462.56
Solubility	≥ 14.05mg/mL in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	DDD107498		

Protocol

Antimalarial experiment [1]:

Malaria parasites	Various malaria parasites
Preparation method	This compound is soluble in DMSO. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.
Reacting condition	0.0001 ~ 10 μM

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Applications	DDD107498 showed excellent inhibition against 3D7 parasites, with the EC50 value of 1.0 nM. It also exhibited similar inhibition against several drug-resistant strains. Besides, DDD107498 was more potent than artesunate against a range of clinical isolates of both P. falciparum and P. vivax with the EC50 values of 0.81 nM and 0.51 nM respectively. In addition, the compound was non-toxic to human MRC5 and Hep-G2 cells at much higher concentrations.

Animal experiment [1]:

Animal models	NOD-scid IL-2R_null mice engrafted with human erythrocytes and infected with P. falciparum strain 3D70087/N9
Dosage form	0.1, 0.3, 0.6, 1 or 3 mg/kg/day; p.o.; for 4 days
Applications	In NOD-scid IL-2R_null mice engrafted with human erythrocytes and infected with P. falciparum strain 3D70087/N9, which were orally dosed daily for 4 days, the ED90 value on day 7 after infection was 0.95 mg/kg/day. Blood sampling from the infected SCID mice suggested the minimum parasiticidal concentration for DDD107498 was 10 ~ 13 ng/mL for asexual blood-stage infections.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

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References:

[1]. Baragaa B, Hallyburton I, Lee MC et al. A novel multiple-stage antimalarial agent that inhibits protein synthesis. Nature. 2015 Jun 18;522(7556):315-20.

Background

DDD107498 is a potent and novel multiple-stage antimalarial agent against multiple life-cycle stages of the Plasmodium parasite. [1]
DDD107498 has an acceptable safety profile and good pharmacokinetic properties. Translation elongation factor 2 (eEF2) has been identified as the molecular target of DDD107498. The factor eEF2 is responsible for the GTP-dependent translocation of the ribosome along messenger RNA, and is essential for protein synthesis. [1]
DDD107498 showed excellent activity against Plasmodium falciparum 3D7 parasites with EC50 value of 1.0 nM, EC90 value of 2.4 nM and EC99 value of 5.9 nM. Furthermore, DDD107498 was more potent than artesunate in ex vivo assays against a range of clinical isolates of both P. falciparum (median EC50 = 0.81 nM (range 0.29–3.29 nM), n = 44) and P. vivax (median EC50 = 0.51 nM (range 0.25–1.39 nM), n = 28) collected from patients with malaria from southern Papua. [1]
DDD107498 showed an EC50 < 1 nM against the liver schizont forms of P. berghei and Plasmodium yoelii. DDD107498 potently inhibited both male and female gamete formation from the gametocyte stage at similar concentrations [1.8 nM (95% CI 1.6–2.1 nM) and 1.2 nM (95% CI 0.8–1.6 nM)] respectively. DDD107498 blocked subsequent oocyst development in the mosquito after 7 days with an EC50 of 1.8 nM. [1]
DDD107498 had a 90% reduction in parasitaemia (ED90) of 0.57 mg/kg after a single oral dose in mice infected with the rodent parasite Plasmodium berghei. When orally dosed daily for 4 days, the ED90 on day 7 after infection was 0.95 mg/kg/day. Blood sampling from the infected SCID (severe combined immunodeficiency) mice suggested a minimum parasiticidal concentration for DDD107498 of 10–13 ng/ml for asexual blood-stage infections. [1]
In contrast, the compound was not toxic to human cells (MRC5 and Hep-G2 cells) at much

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higher concentrations (>20,000-fold selectivity). DDD107498 displayed excellent pharmacokinetic properties in preclinical species, including good oral bioavailability and long plasma half-life. DDD107498 showed good drug-like properties including metabolic stability when incubated with hepatic microsomes or hepatocytes from several species; good solubility in a range of different media; and low protein binding. [1]

Reference:

1.Baragaña B, Hallyburton I, Lee MC et al. A novel multiple-stage antimalarial agent that inhibits protein synthesis. Nature. 2015 Jun 18;522(7556):315-20.

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