Product Data Sheet

Product Name: GSK3186899 (DDD-853651)
Cat. No.: GC33235

Chemical Properties

Cas. No.	1972617-87-0		
SMILES	O=S(CCC(F)(F)F)(N[C@H]1CC[C@H](NC2=NC=C3C(NN=C3N4C[C@H](C)OCC4)=N2)CC1)=O		
Formula	$C_{19}H_{28}F_3N_7O_3S$	M.Wt	491.53
Solubility	Soluble 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	GSK3186899 (DDD-853651)		

Background

GSK3186899 is an inhibitor of cdc-2-related kinase 12 (CRK12), with an EC50 of 1.4 μM for L. donovani in an intra-macrophage assay.

GSK3186899 (Compound 7) is active against L. donovani in an intra-macrophage assay with an EC50 value of 1.4 μM, and shows good selectivity against mammalian THP-1 host cells (EC50 value>50 μM). This is not as potent as reported data for amphotericin B (EC50 value of 0.07 μM in the intra-macrophage assay), but is comparable to the clinically used drugs miltefosine and paromomycin (EC50 values of 0.9 μM and 6.6 μM, respectively). GSK3186899 is also active in cidal axenic amastigote assay (EC50 value of 0.1 μM). At a concentration of 0.2 μM, GSK3186899 is cytocidal at 96 h; increasing the concentration to 1.8 μM reduced this time to 48 h. GSK3186899 demonstrates a less than 10-fold variation in potency against a panel of Leishmania-derived lines. GSK3186899 is also more active in a panel of Leishmania lines using human peripheral blood mononuclear cells as the host cells[1].

In the mouse model of infection, GSK3186899 demonstrates comparable activity to the

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

front-line drug miltefosine, reducing parasite levels by 99% when dosed orally twice a day for 10 days at 25 mg/kg. The efficacy of treatment is dependent on dose, frequency, and duration (10 days better than 5). The non-clinical safety data for GSK3186899 suggests a suitable therapeutic window for progression into regulatory preclinical studies. Non-GLP preclinical assessment of cardiovascular effects and genotoxicity does not reveal any issues that would prevent further development. In addition, there are no notable adverse effects in a rat seven-day repeat-dose oral toxicity study with respect to clinical chemistry and histopathology at all doses tested. Both the in vivo efficacy and safety profile of GSK3186899 support progression to definitive safety studies[1].

[1]. Wyllie S, et al. Cyclin-dependent kinase 12 is a drug target for visceral leishmaniasis. Nature. 2018 Aug;560(7717):192-197.

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Address: 10292 Central Ave. #205, Montclair, CA, USA