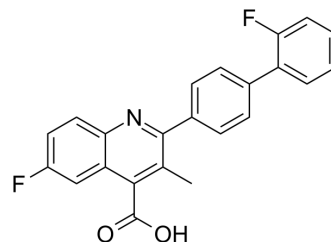


Brequinar

Cat. No.:	HY-108325		
CAS No.:	96187-53-0		
Molecular Formula:	C ₂₃ H ₁₅ F ₂ NO ₂		
Molecular Weight:	375.37		
Target:	Dihydroorotate Dehydrogenase; SARS-CoV; Virus Protease; DNA/RNA Synthesis		
Pathway:	Metabolic Enzyme/Protease; Anti-infection; Cell Cycle/DNA Damage		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro	DMSO : 25 mg/mL (66.60 mM; Need ultrasonic)					
		Solvent Concentration	Mass	1 mg	5 mg	10 mg
	Preparing Stock Solutions	1 mM		2.6640 mL	13.3202 mL	26.6404 mL
		5 mM		0.5328 mL	2.6640 mL	5.3281 mL
10 mM			0.2664 mL	1.3320 mL	2.6640 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: 2.08 mg/mL (5.54 mM); Suspended solution; Need ultrasonic and warming 2. Add each solvent one by one: 10% DMSO >> 90% corn oil Solubility: ≥ 2.08 mg/mL (5.54 mM); Clear solution					

BIOLOGICAL ACTIVITY

Description	Brequinar (DUP785) is a potent inhibitor of dihydroorotate dehydrogenase (DHODH) with an IC ₅₀ of 5.2 nM for human DHODH. Brequinar has potent activities against a broad spectrum of viruses. Brequinar also has an anti-SARS2 activity.
In Vitro	Brequinar reduces virus progeny production by >90%, with EC ₅₀ of 17 nM. Brequinar (5 μM) also inhibits other orthopoxviruses, and blocks virus DNA replication. Brequinar does not affect virus early gene expression, but has a severe effect on the late stage of the virus cycle ^[1] . Brequinar reduces the level of envelope protein production and the viral titer in a dose-dependent manner, with EC ₅₀ of 78 nM in the CFI assay. Brequinar (5 μM) inhibits viral RNA synthesis. Brequinar has antiviral effect, but the effect is reversed by pyrimidine. Brequinar-resistant viruses can be selected in cell culture. Brequinar (5 μM) suppresses the luciferase activities from both the WT and NS5 mutant replicons ^[2] . Brequinar sodium effectively prevents the increase in PyNTP levels with an IC ₅₀ of 0.26 μM. Brequinar sodium effectively inhibits cell proliferation with an

	<p>IC₅₀ of 0.26 μM. Brequinar sodium inhibits autophosphorylation of p56^{lck} with IC₅₀ of 70 μM; inhibition is 39, 41, and 60% for 25, 50, and 100 μM Brequinar sodium, respectively. Brequinar sodium also inhibits the phosphorylation by p56^{lck} of the exogenous substrate, histone 2B, with an IC₅₀ of 70 μM; inhibition is 10, 43, 59, and 86% for 25, 50, 100, and 200 μM Brequinar sodium, respectively. Brequinar sodium inhibits autophosphorylation of p59^{fyn} with an IC₅₀ of 105 μM; inhibition is 0, 17, 48, and 65% for 25, 50, 100, and 200 μM Brequinar sodium, respectively. Brequinar sodium also inhibits the phosphorylation by p59^{fyn} of histone 2B with an IC₅₀ of 20 μM; inhibition is 26, 54, 79, 83, and 84% for 10, 25, 50, 100, and 200 μM Brequinar sodium, respectively^[3].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>Brequinar sodium-treated (10-20 mg/kg/day) mice has a 31% reduction in percentage of packed cell volume compared with untreated BALB/c mice. Brequinar sodium reduces UTP and CTP levels in bone marrow cells by 30 and 25%, respectively. Brequinar sodium (10-20 mg/kg/day) in combination with uridine (1000-2000 mg/kg/day) prevents anemia, and the hematocrits remain at levels (61-63%) comparable with those of untreated controls^[3].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Kinase Assay ^[3]	<p>Immunoprecipitated p59^{fyn} or p56^{lck} from CTLL-4 cells or LSTRA cells (5×10⁶) is preincubated with various concentrations of BQR in the PTK buffer (50 mM HEPES (pH 7.4), 10 mM MgCl₂, and 10 mM MnCl₂) on ice for 10 min. Exogenous substrate, histone 2B (2 μg), is added and, after 10 min, the reaction is initiated by addition of 10 μCi [γ-³²P]ATP. After incubation at 20°C for 10 min, the reaction mixture is subjected to electrophoresis in a 12.5% SDS-polyacrylamide gel. Phosphorylation of the kinase and the exogenous substrate is analyzed by autoradiography.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Cell Assay ^[1]	<p>The neutral-red uptake assay is used to evaluate cell viability. BSC-40 cells are seeded in 96-well plates in the presence of concentrations of Brequinar ranging from 0.01 μM to 75 μM for 24 h. Control cells are incubated with 0.1% DMSO. Neutral red is methanol/acetic acid-extracted from cells and is quantitated at an absorbance of 490 nm (A490). All measurements expressed the average of four independent assays.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[3]	<p>Brequinar is administered once daily by i.p. injection, while uridine is administered twice daily. Mice are bled through the orbital vein using a microhematocrit capillary tube, and the blood is centrifuged for 10 min at 550 × g. The percentage of packed cell volumes is determined with a microhematocrit capillary tube reader. All mice are killed 4 h after receiving their last dose of Brequinar or uridine.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

CUSTOMER VALIDATION

- Nature. 2022 Apr;604(7904):134-140.
- J Med Chem. 2020 Jul 23;63(14):7633-7652.
- Viruses. 2021 Jun 28;13(7):1255.
- Research Square Preprint. 2020 Dec.

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- [3]. Xu X, et al. In vitro and in vivo mechanisms of action of the antiproliferative and immunosuppressive agent, brequinar sodium. *J Immunol.* 1998 Jan 15;160(2):846-53.
- [4]. Zeping Zuo, et al. Bifunctional Naphtho[2,3-d][1,2,3]triazole-4,9-dione Compounds Exhibit Antitumor Effects In Vitro and In Vivo by Inhibiting Dihydroorotate Dehydrogenase and Inducing Reactive Oxygen Species Production. *J Med Chem.* 2020 Jun 4.
- [5]. David C Schultz, et al. Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2. *Nature.* 2022 Feb 7.
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