Brequinar

Cat. No.: HY-108325

CAS No.: 96187-53-0

Molecular Formula: $C_{23}H_{15}F_2NO_2$

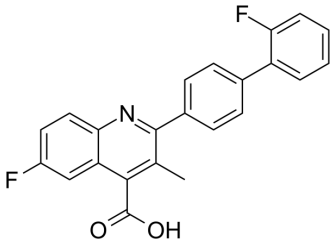
Molecular Weight: 375.37

Target: Virus Protease; Dihydroorotate Dehydrogenase; DNA/RNA Synthesis; SARS-CoV

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

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (66.60 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	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

	IC_{50} of 0.26 μM. Brequinar sodium inhibits autophosphorylation of $p56^{lck}$ with IC_{50} 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 IC_{50} 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 IC_{50} 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 IC_{50} of 20 μM; inhibition is 26, 54, 79, 83, and 84% for 10, 25, 50, 100, and 200 μM Brequinar sodium, respectively[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [3]	Immunoprecipitated $p59^{fyn}$ or $p56^{lck}$ from CTLL-4 cells or LSTRA cells (5×10^6) is preincubated with various concentrations of BQR in the PTK buffer (50 mM HEPES (pH 7.4), 10 mM $MgCl_2$, and 10 mM $MnCl_2$) 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-^{32}P]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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2024 Feb;626(7998):411-418.
- Nature. 2022 Apr;604(7904):134-140.
- Nat Cell Biol. 2023 Jun;25(6):836-847.
- Adv Sci (Weinh). 2022 May 4;e2105451.
- Sci Adv. 2022 Sep 16;8(37):eabp9005.

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REFERENCES

[1]. Schnellrath LC, et al. Potent antiviral activity of brequinar against the emerging Cantagalo virus in cell culture. Int J Antimicrob Agents. 2011 Nov;38(5):435-41.

[2]. Qing M, et al. Characterization of dengue virus resistance to brequinar in cell culture. Antimicrob Agents Chemother. 2010 Sep;54(9):3686-95.

[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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