

Product Data Sheet

Product Name: PF-07321332

Cat. No.: GC62631

Chemical Properties

Cas. No. 2628280-40-8

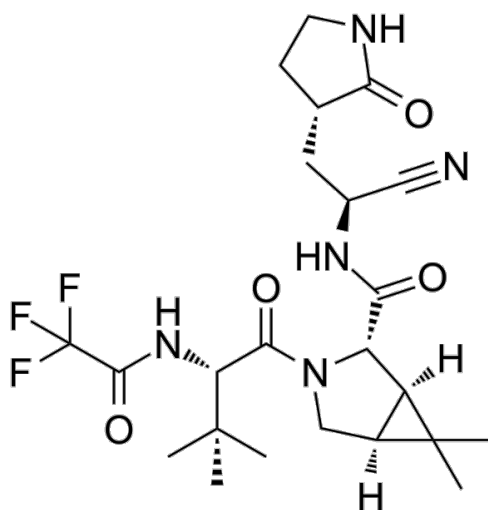
Formula $C_{23}H_{32}F_3N_5O_4$ M.Wt 499.53

Solubility DMSO : 140 mg/mL (280.26 mM; Need ultrasonic) Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C 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



Protocol

Cell experiment [1]:

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Cell lines differentiated normal human bronchial epithelial (dNHBE) cells

The dNHBE cells were grown on trans-well inserts consisting of approximately 1.2×10^6 cells in MatTek's proprietary culture medium added to the basolateral side, with the apical side exposed to a humidified 5% CO₂ environment at 37 °C. On day 1, dNHBE cells were infected with SARS-CoV-2 strain USA-WA1/2020 at a MOI of approximately 0.0015 50% of the cell culture infectious dose (CCID₅₀)

Preparation Method per cell, and PF-07321332 treatment was carried out by inclusion of drug dilutions in basolateral culture media. At day 3 and day 5, virus released into the apical compartment was harvested by the addition of 0.4 ml culture media. The virus titer was then quantified by infecting Vero76 cells in a standard endpoint dilution assay and virus dose that was able to infect 50% of the cell cultures (CCID₅₀ per ml) was calculated.

Reaction Conditions 0.1-10000 nM for 3 days

Applications Treatment of dNHBE cells with varying concentrations of PF-07321332 for 3 days led to inhibition of SARS-CoV-2 viral replication, with EC₅₀ and EC₉₀ values of 61.8 and 181 nM, respectively.

Animal experiment [2]:

Animal models 8-week old female Charles River mice

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Pharmacokinetics studies were performed in an animal biosafety level 2 (ABSL2) facility. A total of 24 BALB/c mice were divided into 4 groups: group 1: untreated, infected control; group 2: 300 mg/kg PF-07321332; group 3: 1000 mg/kg PF-07321332, and group 4: untreated, uninfected control (for pharmacokinetic analysis and normal weight). Mice were anesthetized by intraperitoneal (i.p.) injection of ketamine/xylazine (50 mg/kg/5 mg/kg) and inoculated intranasally (i.n.) with 1×10^5 50% CCID₅₀ of SARS-CoV-2 MA10 (90 ml/nares).

Dosage form 300,1000 mg/kg, i.p. ; 300,1000 mg/kg, BID, po.

Applications PF-07321332 limits cellular infiltration and protects lung tissue from damage caused by virus replication.

References:

[1]: Owen D R, Allerton C M N, Anderson A S, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19[J]. Science, 2021, 374(6575): 1586-1593.

Background

PF-07321332 (Nirmatrelvir) is an orally administered severe acute respiratory syndrome coronavirus 2 main protease (Mpro) inhibitor with potent pan-human-coronavirus activity in vitro [1]. PF-07321332 inhibited activity against SARS-CoV-2 Mpro with the IC₅₀ value of 0.023 μ M [2].

PF-07321332 demonstrated potent inhibition in FRET Mpro assays representing Mpro from all coronavirus types known to infect humans [3,4,5], including beta-coronaviruses (SARS-CoV-2, SARS-CoV-1, HKU1, OC43, and MERS-CoV) as well as alpha-coronaviruses (229E and NL63) [6]. At the concentration tested (100 μ M) of PF-07321332, no inhibitory effects were noted against several mammalian cysteine (caspase 2, cathepsin B, and cathepsin L), serine (chymotrypsin, elastase, and thrombin) and aspartyl (cathepsin D) proteases [6]. Treatment of dNHBE cells with varying concentrations of PF-07321332 for 3 days led to inhibition of SARS-CoV-2 viral replication,

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with EC50 and EC90 values of 61.8 and 181 nM, respectively [6].

After infection with SARS-CoV-2 MA10, mice treated twice daily with PF-07321332 (at both 300 and 1000 mg/kg doses) were protected from weight loss compared with vehicle-treated mice. At 4 days after infection, mice were sacrificed and lung viral titers were evaluated in CCID50 assays. Infected animals in the placebo group had robust infection in the lungs, whereas virus levels in mice treated with PF-07321332 were significantly reduced (300 and 1000 mg/kg PF-07321332-treated groups, respectively) [6]. PF-07321332 exhibited moderate plasma clearance (CL_p) in rats and monkeys, with elimination half-lives (t_{1/2}) of 5 hours and <1 hour, respectively, after intravenous dosing [6].

References:

- [1]. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19[J]. New England Journal of Medicine, 2022, 386(15): 1397-1408.
- [2]. Li J, Lin C, Zhou X, et al. Structural Basis of the Main Proteases of Coronavirus Bound to Drug Candidate PF-07321332[J]. Journal of Virology, 2022, 96(8): e02013-21.
- [3]. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China[J]. Nature, 2020, 579(7798): 265-269.
- [4]. Zhou P, Yang X L, Wang X G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin[J]. nature, 2020, 579(7798): 270-273.
- [5]. Cui J, Li F, Shi Z L. Origin and evolution of pathogenic coronaviruses[J]. Nature reviews microbiology, 2019, 17(3): 181-192.
- [6]. Owen D R, Allerton C M N, Anderson A S, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19[J]. Science, 2021, 374(6575): 1586-1593.

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