3CLp dimer binds 3CLp inhibitors

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 81

This document contains 1 reaction (see Table of Contents)

https://reactome.org
3CLp dimer binds 3CLp inhibitors

Stable identifier: R-HSA-9694592

Type: uncertain

Compartments: cytosol

Diseases: COVID-19

The rep proteases that are essential for viral polyprotein processing by the coronaviruses and enteroviruses exhibit a strong preference for substrates containing Gln at P1 position, and share an active-site conformation that engages the substrate's P1 residue. PF-00835231, compound 11r and compound 13b are peptidomimetic α-ketoamides that function as high-affinity non-cleavable substrate analogues and thus exhibit antiviral activity against dimeric 3C-like proteinases (3CLp dimer) of coronaviruses and enteroviruses (Chen et al. 2005, Zhang et al. 2020). Nirmatrelvir contains the amide as part of a heterocycle and is optimized for oral delivery (Vandyck & Deval, 2021).

The clinical safety and efficacy of α-ketoamides in Covid-19 are under investigation. The compound PF-00835231 is in a phase I trial NCT04535167 (as phosphate prodrug), and nirmatrelvir was the subject of the phase I trial NCT04756531 that showed plasma concentrations were considerably above the SARS-CoV-2 antiviral EC90 value (Owen et al, 2021). In the followup phase 2/3 trial (NCT04960202) interim analysis the drug was found to reduce the risk of hospitalization or death by 89% compared to placebo. This lead to emergency approval of the combination with ritonavir as Paxlovid.

In addition to α-ketoamides other compounds inhibit 3C-like proteinases.

Boceprevir, narlaprevir, simeprevir, telaprevir and vaniprevir are hepatitis C drugs that inhibit HCV nsp3 protease, as well as SARS-CoV-2 3CLp (Ma et al, 2020; Lo et al, 2020; Anson et al, 2020; Kneller et al, 2020; Bafna et al, 2021; Jan et al, 2021). Nelfinavir is an HIV protease inhibitor that also inhibits nsp3 at IC50 of 118 ± 18 µM (Jan et al, 2021). However, nelfinavir mesylate exhibited 15-fold higher anti-SARS-CoV-2 activity than boceprevir due to Spike inhibition (Musarrat et al, 2020).

Suramin is used to treat African sleeping sickness and river blindness, the mechanism of which is not clear. It inhibits nsp3 at an IC50 of 6.5 µM (Zhu et al, 2020). Baicalin and baicalein are natural flavonoids from Scutellaria species, used in folklore medicine and were investigated in phase I trials. They inhibit nsp3 at IC50 of 6.41 ± 0.95 µM, and 0.94 ± 0.20 µM respectively (Su et al, 2020). Ebselen is a mimic of glutathione peroxidase with antioxidant activity. In two studies inhibition of SARS-CoV-2 PLpro protease (nsp3) and 3CLp was shown. This was not confirmed, however, in a third study (Jin et al, 2020; Tomczak et al, 2021; Gurard-Levin et al, 2020).

Literature references


**Editions**

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