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Drug development against Mac1 from SARS-CoV-2 through crystallographic fragment screening

Viral macrodomains are an important pathogenicity factor during infection with coronaviruses, including SARS-CoV-2. These proteins are ADP-ribosyl hydrolases that bind and remove ADP-ribosylation, a post-translational modification that is associated with the innate immune response against viral infection. The non-structural protein 3 (nsP3) of SARS-CoV-2 includes such a macrodomain, known as Mac1, which has a de-mono-ADP-ribosylating (de-MARylation) activity that is important for viral replication and promotes immune evasion. Indeed, studies in other coronaviruses have also shown that mutations affecting this function lead to reduced pathogenicity, making Mac1 an attractive target for the development of small molecule inhibitors.

Here, we have used the crystallographic fragment screening pipeline at HZB to find small molecules that bind to Mac1. Screening was performed using two 96 compound libraries: the F2X-Entry library, a fragment library developed at the Helmholtz Zentrum Berlin, and the KIT library, a novel fragment library developed in collaboration with the Karslruhe Institute of Technology (KIT). With this approach, we have identified several promising hits in the active site of Mac1. In addition, we have experimentally screened compounds selected by KIT through virtual screening of their molecule archive against Mac1, which, taken together, gives us numerous starting points that show great potential to be developed into lead-like molecules against SARS-CoV-2.

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