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Massive X-ray screening against SARS-CoV-2 main protease

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As a response to the SARS-CoV-2 pandemic we have set up a large consortium of more than one hundred scientist centered at DESY in Hamburg in order to find suitable drug candidates. In contrast to common screening techniques such as biochemical activity-based assays or X-ray fragment screening, here we employed massive X-ray crystallographic screening of two drug-repurposing libraries against the SARS-CoV-2 main protease (Mpro) as initial target. In total co-crystallization experiments of 5953 individual drugs with Mpro were setup and datasets from more than 8000 crystals were collected at the PETRA III MX beamlines. Our screening effort resulted in the identification of 37 compounds binding to Mpro. Secondary screening of these hits in a cell-based viral infection assay carried out at the Bernhard Nocht-Institute revealed antiviral activity in combination with low cytotoxicity for six compounds, which have not yet been reported as inhibitors of SARS-CoV-2. While four of these inhibitors bind to the catalytic site of the enzyme, the remaining two bind to a previously undescibed allosteric site within the dimerization domain [1]. For the two most promising compounds from our screen, Calpeptin and Pelitinib, we have intiated further preclinical testing

References:
[1] S. Günther, P. Y. A. Reinke, et al. , bioRxiv, doi:10.1101/2020.11.12.378422.

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