Severe acute respiratory syndrome coronaviruses 1 and 2 (SARS-CoV-1 and SARS-CoV-2) have become a major threat to global public health. Their 3C-like main protease (Mpro) presents structural similarity to the active site domain of enterovirus 3C protease and it is one of the best-characterized coronavirus drug targets. We studied the antiviral activity of the orally bioavailable enterovirus protease covalent inhibitor AG7404 and its related molecule rupintrivir against SARS-CoV-1 and SARS-CoV-2 from a structural, biochemical, and cellular perspective. The crystallographic structures of AG7404 in complex with SARS-CoV-1 Mpro and SARS-CoV-2 Mpro and of rupintrivir in complex with SARS-CoV-2 Mpro were solved (Figure 1). The structural data allowed a detailed analysis of protein-inhibitor interactions, which indicates that AG7404 has a better fit to the active site of the target protease than rupintrivir. This observation was further confirmed by biochemical FRET assays. The antiviral activity of the two compounds against SARS-CoV-2 was confirmed in a human cell culture model of SARS-CoV-2 infection [1].

Additional structural and biochemical studies aiming to unveil the catalytic mechanism of the main protease are currently being performed, together with the analysis of a number of structures in complex with substrate peptides belonging to human proteins. The cleavage of such proteins, which are involved in host innate immune response mechanisms, has been suggested to play a role in the pathophysiology of COVID-19, which includes an enhanced production of cytokines and inflammatory response [2].
