A POTENT THIAZOLYL KETONE INHIBITOR OF SARS-CoV-2 MAIN PROTEASE (M^{pro})

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The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has had a profound impact on global health, causing more than 750 million cases and nearly 7 million deaths worldwide up to now. With limited therapeutic options available, the development of novel agents to combat COVID-19 is crucial to address the ongoing challenges of the disease. In 2021, Pfizer reported a nitrile inhibitor (PF-07321332) of SARS-CoV-2 main protease (M^{pro}), which has been approved by FDA for clinical use, along with α-ketobenzothiazole inhibitors [1]. Furthermore, additional peptidomimetic α-ketobenzothiazoles have been proposed as SARS-CoV-2 M^{pro} inhibitors [2]. In the present study, we explore for the first time a thiazolyl ketone as the warhead in SARS-CoV-2 M^{pro} inhibitors. Two such thiazolyl ketones were synthesized and tested *in vitro* against SARS-CoV-2 M^{pro}. Compound GK729 (Figure 1), containing a Leu residue at P2 position and a glutamic acid surrogate at P1, exhibited promising results. Elongation of the peptide chain by Val afforded compound GK730, which exhibited excellent inhibitory potency. The stability of the enzyme-compound complex was also investigated for the most promising compound, GK730. The crystal structure of the SARS-CoV-2 M^{pro} complex with GK730 revealed the key interactions. Thus, thiazolyl ketone GK730 has been identified as a novel potent inhibitor of SARS-CoV-2 M^{pro}.

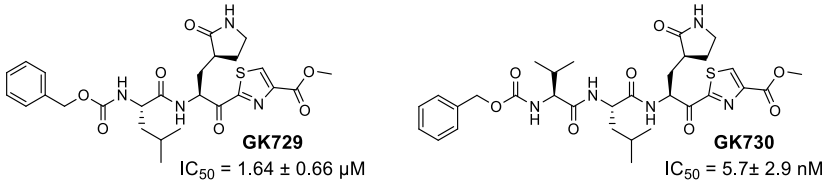

Figure 1. Thiazolyl ketone inhibitors of SARS-CoV-2 M^{pro}.

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References

[1] D. R. Owen *et al*., *Science* **2021**, *374*, 1586-1593.

[2] S. Konno *et al*., *J. Med. Chem.* **2022**, *65*, 2926-2939.