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Discovery of pyrrolo[2,3-*d*]pyrimidin-4-one derivative YCH3124 as a potent USP7 inhibitor for cancer therapy

Zhen Zhuang, Yu-Ling Miao, Shan-Shan Song, Guang-Tong Leng, Xiao-Fei Zhang , Qian He, Jian Ding, Jin-Xue He*, and Chun-Hao Yang.*

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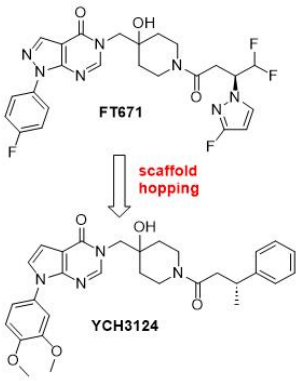

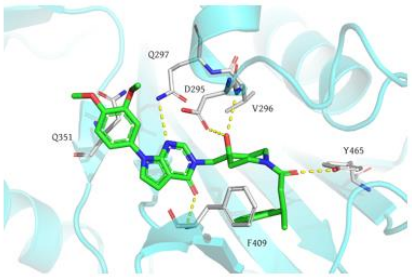

Compound	USP7 IC_{50}/nM	MM1.S IC_{50}/nM	CHP-212 IC_{50}/nM	LNCaP IC_{50}/nM	MV-4-11 IC_{50}/nM
YCH3124	41.8 ± 3.6	10.7 ± 3.1	9.9 ± 0.5	3.6 ± 1.8	52.3 ± 9.9
FT671	64.6 ± 4.1	98.1 ± 7.1	61.6 ± 1.8	40.3 ± 1.5	212.8 ± 17.4

Abstract: USP7 is one of the most studied deubiquitinating enzymes, which is involved in the regulation of multiple cell signaling pathways and has been shown to be associated with the occurrence and progression of a variety of cancers. Inhibitors targeting USP7 have been studied by several teams, but most of them lack selectivity and have low activities. Herein, we reported a serious of pyrrole[2,3-*d*]pyrimidin-4-one derivatives through scaffold hopping of recently reported 4-hydroxypiperidine compounds. The representative compound Z33 (YCH3124) exhibited highly potent USP7 inhibition activity as well as anti-proliferative activity against four kinds of cancer cell lines. Further study revealed that YCH3124 effectively inhibited the downstream USP7 pathway and resulted in the accumulation of both p53 and p21 in a dose-dependent manner. Notably, YCH3124 disrupted cell cycle progression through restricting G1 phase and induced significant apoptosis in CHP-212 cells. In summary, our efforts provided a series of novel pyrrole[2,3-d]pyrimidin-4-one analogs as potent USP7 inhibitors with strong anti-cancer activity.