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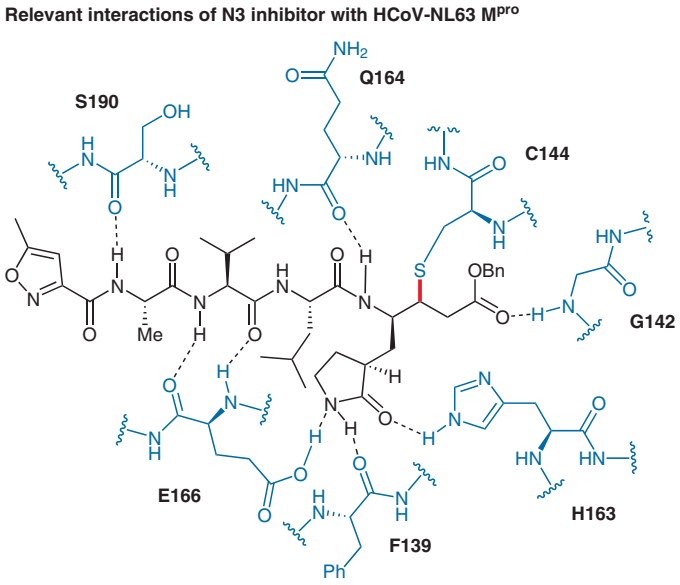
Structure of Main Protease from Human Coronavirus NL63: Insights for Wide Spectrum Anti-Coronavirus Drug Design
Sci. Rep. **2016**, *6*, DOI: 10.1038/srep22677.

Crystal Structure of the Main Protease of Human Coronavirus NL63



Significance: CoVs are the causative agents responsible for several respiratory syndromes including SARS, MERS, and COVID-19. There are no known treatments for CoV-related ailments currently. The substrate-binding site of the various CoV main proteases (M^{pro}) have high sequence homology and therefore represent an attractive target for the development of broad-spectrum anti-CoV therapies. In 2016, Yang and co-workers disclosed the crystal structure of the HCoV-NL63 (a human CoV) main protease (M^{Pro}) complexed with the covalent inhibitor N3, providing a structural basis for the pharmacological inhibition of CoV M^{pro} that may have relevance for the ongoing SARS-CoV-2 pandemic.

Comment: The M^{pro} inhibitor N3 is a covalent inhibitor designed as an active site mimic for the TGEV M^{pro} autoprocessing site. The crystal structure of the HCoV-NL63 M^{pro} reveals multiple H-bond contacts between residues E166, F129, H163, G142, Q164, and S190. The α,β-unsaturated ester of N3 forms a covalent adduct with cysteine 144, validating the mechanism of inhibition of HCoV-NL63 M^{pro} by N3. Sequence alignment of the HCoV-NL63 M^{pro} with six related human and animal CoVs main proteases revealed that they had high sequence homology in the substrate binding site, suggesting that this class of inhibitor may serve as a lead compound for anti-Cov therapeutics.

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Synfacts 2020, 16(06), 0715 Published online: 15.05.2020
DOI: 10.1055/s-0040-1706955; **Reg-No.:** T04520SF

Category
Chemistry in Medicine and Biology

Key words
X-ray crystal structure
coronavirus
pharmacology