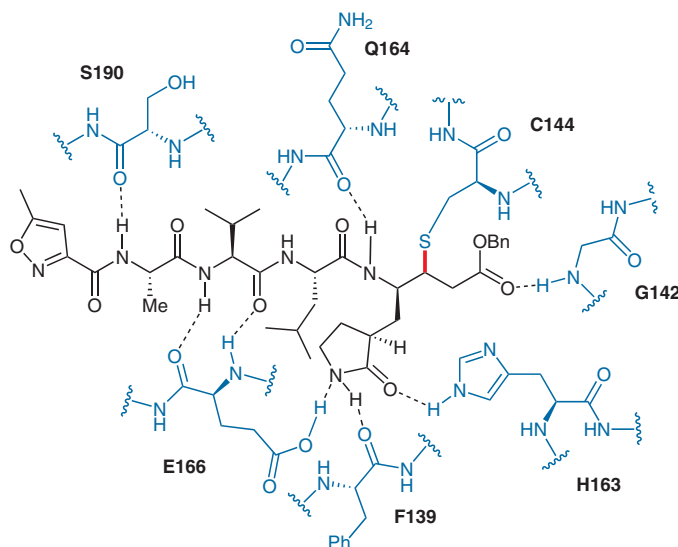


## Crystal Structure of the Main Protease of Human Coronavirus NL63

Relevant interactions of N3 inhibitor with HCoV-NL63 M<sup>Pro</sup>



**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<sup>Pro</sup>) 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<sup>Pro</sup>) complexed with the covalent inhibitor N3, providing a structural basis for the pharmacological inhibition of CoV M<sup>Pro</sup> that may have relevance for the ongoing SARS-CoV-2 pandemic.

**Comment:** The M<sup>Pro</sup> inhibitor N3 is a covalent inhibitor designed as an active site mimic for the TGEV M<sup>Pro</sup> autoprocessing site. The crystal structure of the HCoV-NL63 M<sup>Pro</sup> reveals multiple H-bond contacts between residues E166, F129, H163, G142, Q164, and S190. The  $\alpha,\beta$ -unsaturated ester of N3 forms a covalent adduct with cysteine 144, validating the mechanism of inhibition of HCoV-NL63 M<sup>Pro</sup> by N3. Sequence alignment of the HCoV-NL63 M<sup>Pro</sup> 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.

Category

Chemistry in  
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Key words

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