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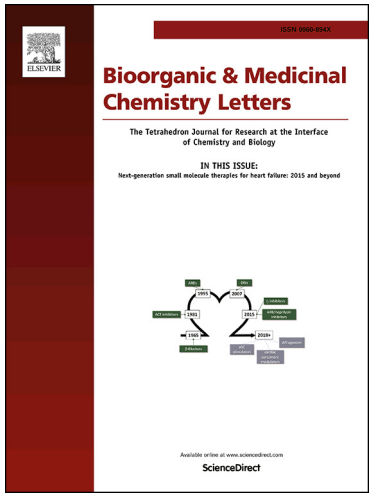

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Synthesis, biological evaluation and molecular modeling of a novel series of fused 1,2,3-triazoles as potential anti-coronavirus agents

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Abstract

Synthesis and biological evaluation of a novel library of fused 1,2,3-triazole derivatives are described. The in-house developed multicomponent reaction based on commercially available starting materials was applied and broad biological screening against various viruses was performed, showing promising antiviral properties for compounds **14d**, **14n**, **14q**, **18f** and **18i** against human coronavirus 229E. Further *in silico* studies identified the key molecular interactions between those compounds and the 3-chymotrypsin-like protease, which is essential to the intracellular replication of the virus, supporting the hypothesis that the protease is the target molecule of the potential antiviral derivatives.

Keywords: Respiratory Syndrome, Coronavirus, 3CL protease, 1,2,3-triazole, biological evaluation

Coronaviruses are single-stranded RNA viruses associated with mild to severe respiratory symptoms. Human coronaviruses (HCoV) strains HCoV-229E and HCoV-OC43 were first described in the 1960s as causes for respiratory tract infections in humans, including common cold and pneumonia.[1] In 2002-2003, a new human coronavirus, named SARS-CoV, was identified as the etiological agent for the global outbreak of severe acute respiratory syndrome (SARS), which caused the death of over 800 individuals among 8000 cases worldwide, representing a fatality rate of almost 10%.[2,3,4] Since then three additional coronaviruses have been recognized. Initially, HCoV-NL63 [5] and HCoV-HKU1,[6] were reported causing acute respiratory diseases of lower severity compared to the SARS-CoV and more recently, Middle East respiratory syndrome (MERS-CoV) causing lethal respiratory diseases.[7,8] To date, there are no approved antiviral drugs or vaccines available for the prevention and/or treatment of SARS-like viruses making the development of effective antiviral agents an imperative need.[9]

Coronaviruses express two proteases, a papain-like protease (PL^{pro}) and a 3-chymotrypsin-like protease ($3CL^{pro}$). The $3CL^{pro}$ enzyme, also referred to as Main protease (M^{pro}), is essential to the intracellular viral replication, making it an attractive target for the development of novel inhibitors.[10] Reports in the literature