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Selenosemicarbazones as new inhibitors of the main proteases of SARS-CoV-2

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Severe acute respiratory syndrome β-coronavirus 2 (SARS-CoV-2) is the causal agent of the coronavirus disease first reported in 2019 (COVID-19). It is the third epidemic triggered by a coronavirus that evolved in recent years after the spread of SARS-CoV in 2002, and Middle East respiratory syndrome (MERS-CoV) that spread in 2012. SARS-CoV-2 produces a spike protein that binds to host cell receptor ACE2 for entry.[1] Upon entry, the positive genomic RNA of SARS-CoV-2 will attach directly to the host ribosome and translate two large polyproteins, which are then processed by proteolysis into components for packaging new virions. This proteolysis is controlled by two protease enzymes, the coronavirus main protease (Mpro) and the papain-like protease (PLpro). These proteins are essential for viral replication, they are considered attractive drug targets for treating coronaviruses.

Due to the great similarity of the active site of 3CLpro between different variants of SARS-CoV-2, as well as other coronaviruses, inhibitors of this protease have the potential to act as broad-spectrum agents. of these, 3CLpro has been widely called the virus' "Achilles' Heel" and is considered one of the most attractive targets for drug development against SARS-CoV-2.

The similarity between 3CLpro and other cysteine proteases triggered our interest since previous works by our group identified a large number of thio and selenosemicarbazone derivatives with good inhibitory activity of cruzipain (Ki in the ηM range), the cysteine protease of the parasite Trypanosoma cruzi moreover, structurally related compounds like Ebselen

(IC50 = 0.67 M) and Disulfiram (IC50 = 9.35 M) have been described as in vitro inhibitors of 3CLpro. They contain in their structure N, S and Se with similar connectivity to thio and selenosemicarbazones.

Furthermore, selenosemicarbazones have been described bearing diverse biological activities as antitumoral or chemo preventive, antiviral, antibacterial, antifungal, antiparasitic and neuroprotective.

In this work we selected an in-house collection of 30 thio and selenosemicarbazones (SeSC) designed as cruzipain inhibitors, and focused on the screening of 3CLpro and PLpro enzymes. The results indicated that four selenosemicarbazones and one thiosemicarbazone showed 3CLpro IC50 < 10 M while also four were active against PLpro. We next turned to the evaluation of the antiviral activity of the most promising compounds. The efficacy of the compounds against infectious SARS-CoV-2 virus (Wuhan strain) in Vero E6 cells was evaluated and the selectivity Index was calculated. Interestingly three selenosemicarbazones showed IC50 < 1 M, with SI between 40 and 63. In order to compute physicochemical descriptors as well as to predict ADME parameters, pharmacokinetic properties, druglike nature and medicinal chemistry friendliness of the SeSC tested, we used

SwissADME web tool. The results suggest that compounds would have good drug likeness properties and ADME parameters.

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Biography

Graciela Mahler, PhD, Professor of Organic Chemistry was born in Paysandú Uruguay. She Started out in education for Chemistry for some years. Bachelor of Science, Chemistry – 1992, Universidad de la República (UdelaR), Montevideo, Uruguay. 2003 she got her PhD in organic chemistry, Montevideo UdelaR and in 2004 was a pos doc at the Chemistry Department, University of Pittsburgh. Since 2005 is a professor at the University of the Republic. Over the last 17 years her main scientific interest includes the development of enzyme inhibitors using different tools like: dynamic combinatorial chemistry, bioisosterism and virtual screening. She focuses on the development of new synthetic methodologies for the rapid generation or molecular complexity to evaluate it bioactivity against trypanosomatids, helmints, viruses and bacteria. Awards: Researcher level II of the National Agency of Research and Innovation (ANII) (2015 to present), Member of the PEDECIBA council (2021 to present), Thieme Chemistry Journal Award (2013).

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