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Synthesis, molecular docking, and *in silico* ADME/Tox profiling studies of new 1-aryl-5-(3-azidopropyl)indol-4-ones: Potential inhibitors of SARS CoV-2 main protease

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ABSTRACT

The virus SARS CoV-2, which causes the respiratory infection COVID-19, continues its spread across the world and to date has caused more than a million deaths. Although COVID-19 vaccine development appears to be progressing rapidly, scientists continue the search for different therapeutic options to treat this new illness. In this work, we synthesized five new 1-aryl-5-(3-azidopropyl)indol-4-ones and showed them to be potential inhibitors of the SARS CoV-2 main protease (3CLpro). The compounds were obtained in good overall yields and molecular docking indicated favorable binding with 3CLpro. *In silico* ADME/Tox profile of the new compounds were calculated using the *SwissADME* and *pkCSM-pharmacokinetics* web tools, and indicated adequate values of absorption, distribution and excretion, features related to bioavailability. Moreover, low values of toxicity were indicated for these compounds. And drug-likeness levels of the compounds were also predicted according to the Lipinski and Veber rules.

1. Introduction

In December 2019, a contagion of atypical and severe pneumonia was first reported in Wuhan, Hubei Province, China and has since widely spread worldwide [1]. This new disease was subsequently attributed to a new class of coronavirus, specifically severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), which probably emerged as a zoonotic disease from bats or pangolins, and was named coronavirus disease 2019 (COVID-19) [2]. By the end of January 2020 the outbreak was declared a Public Health Emergency of International Concern by the World Health Organization [3].

COVID-19 causes symptoms such as dry cough, headache, fever, difficult breathing (dyspnea), and pneumonia, which can trigger respiratory failure and as a result death [4]. To date, no highly effective therapy for treating coronavirus infections has been made available, so many research groups worldwide are working to develop therapeutic options to fight this pathogen. Some structural elements of SARS CoV-2 have been identified *in silico* as possible therapeutic targets [5–7]. The most promising targets so far identified have been the spike protein, RNA-dependent RNA polymerase (RdRp), and the papain-like protease 3CLpro, also known as main protease (Mpro) [8,9]. Mpro is interesting because it is fundamental for the life cycle of SARS CoV-2 [2] and the absence of homologous proteins in humans make it an attractive target for the development of new antiviral drugs.

The catalytic site of 3CLpro is a dimeric unit containing a Cys-Hys dyad [10]. The thiol group in Cys acts as a nucleophile in the proteolytic process. So the inhibition of 3CLpro can be achieved using peptidic inhibitors containing electrophilic groups such as epoxides, ketones, aldehydes and Michael acceptors [11].

In this context, organic azides (R-N_3) are groups with an electrophilic behavior. As illustrated in Scheme 1, the nitrogen directly attached to the organic group (labeled **a**) can work as a nucleophile and the distal nitrogen (**c**) shows electrophilic reactivity [12]. Zidovudine is an example of an antiviral containing the azide group, and the presence of the –N_3 functional group (specifically the presence of nitrogen **c**) is determinant for the interaction of the antiviral with its reverse transcriptase pharmacological target [13,14].

Also, indolones constitute an important family of fused heterocycles with potential for use against SARS CoV-2. They are found in many natural products [15] and drugs [16], and show diverse biological

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