In Silico Study of Coumarins and Quinolines Derivatives as Potent Inhibitors of SARS-CoV-2 Main Protease

Yañez, O.
Osorio, M.I.
Uriarte, E.
Areche, C.
Tiznado, W.
Pérez-Donoso, J.M.
García-Beltrán, O.
González-Nilo, F.

Abstract
The pandemic that started in Wuhan (China) in 2019 has caused a large number of deaths, and infected people around the world due to the absence of effective therapy against coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2). Viral maturation requires the activity of the main viral protease (M^{pro}), so its inhibition stops the progress of the disease. To evaluate possible inhibitors, a computational model of the SARS-CoV-2 enzyme M^{pro} was constructed in complex with 26 synthetic ligands derived from coumarins and quinolines. Analysis of simulations of molecular dynamics and molecular docking of the models show a high affinity for the enzyme ($\Delta E_{binding}$ between −5.1 and 7.1 kcal mol^{-1}). The six compounds with the highest affinity show K_d between 6.26×10^{-6} and 17.2×10^{-6}, with binding affinity between −20 and −25 kcal mol^{-1}, with ligand efficiency less than 0.3 associated with possible inhibitory candidates. In addition to the high affinity of these compounds for SARS-CoV-2 M^{pro}, low toxicity is expected considering the Lipinski, Veber and Pfizer rules. Therefore, this novel study provides candidate inhibitors that would allow experimental studies which can lead to the development of new treatments for SARS-CoV-2.

Author keywords
Coumarins
molecular dynamics
protease
quinolines
SARS-CoV-2