Poster

CRIBADO DE ALTO RENDIMIENTO (HTS) DE UNA LIBRERÍA DE PEQUEÑAS MOLÉCULAS PARA LA IDENTIFICACIÓN DE moléculas anti-EBOV

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ABSTRACT

Motivation: Ebola virus (EBOV) is considered as the prototypical pathogen of viral hemorrhagic fever, causing severe disease and mortality rates as high as 90%. The implementation of different High-Throughput Screening systems to avoid the use of BSL-4 facilities will promote the generation of lead molecules and so the development of new therapeutics for EBOV within the next few years. The goals of the present project are directed to the discovery of new antiviral drugs against EBOV by using HTS of different libraries of small compounds, some of which have previously been an excellent source of potent antiviral compounds, by the use of a retroviral pseudotype particle (pEBOV-GFP) carrying the EBOV glycoprotein (GP).

Methods: Retroviral pseudotypes were generated by the transfection with the HIV gag-pol plasmid, pCMV-Δ8.91, the EBOV GP expression construct, pCAGGS-EBOV, and the green fluorescence protein (GFP) reporter construct, pCSGW at a ratio of 1.1:0.5:0.75 (core:envelope:reporter). At we carryed out at the IBiS the screening of different libraries of small compounds of different nature. The libraries of small compounds to be screened were synthesized by: i) the Medicinal Chemistry Institute of Madrid (IQM-CSIC), ii) the Unit of Molecular Chemistry and Pharmacology of the Institute for Research in Biomedicine of Barcelona (IRB), and iii) the Group of Organic Chemistry at the Faculty of Pharmacy of the University of Seville. Antiviral activivity was evaluated by pEBOV-mediated GFP expression.

Results: After the evaluation of 60 compounds, only compounds 4, 10, 17, 23, 33, 34, 125, 126, 279, 284, 298, 372, 385, 414 and 42 showed a significant (> 50%) inhibition of pEBOV-GFP entry (50 µM), presenting values of cytotoxicity (CC50) greater than 100 mM, therefore considered safe. Compounds 21, 371, 82, despite showing optimal inhibition percentages at 50 µM, presented CC50 values lower than our 100 µM threshold and because of that they were excluded from further evaluations.

Conclusions: Although the antiviral activity of molecules identified by these system has to be confirmed against the wild-type EBOV, it is a useful tool to identify anti-EBOV candidates that also solves the necessity of work in BSL-4 facilities. Compounds identified in this work could potentially represent strong hit compounds for the development of a treatment for the EBOV disease.

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