Inhibition of Hepatitis C Virus NS3 ATPase and helicase activities by new compounds


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Hepatitis C virus (HCV) infects 170 to 200 million people worldwide, and constitutes the major agent of chronic non-A and non-B hepatitis. The lack of efficient methods for the treatment of hepatitis C that target proteins or the viral RNA specifically, added to its high chronicity rate make it the cause of many deaths and hepatic transplants annually. The NS3 protein is considered an important target for the development of anti-HCV therapies, since the serine-protease activity (at its N-terminal portion) and the RNA helicase/NTPase activities (at its C-terminal portion) are essential for viral replication and proliferation. In this study, the NS3 helicase/NTPase domain was expressed, purified, and inhibitors screens were performed with 325 compounds against both ATPase and helicase activities. The amount of inorganic phosphate released by ATP hydrolysis and its inhibition were measured by a colorimetric assay, and double-stranded DNA unwinding assays were performed using molecular beacons. Our studies showed that five compounds inhibited both activities and presented dose response, with IC50% values between 13 to 166µM for ATPase activity, and 45 to 261µM for helicase activity. Besides, three of these compounds seem to be non-competitive inhibitors of the NS3 helicase ATPase activity, suggesting that they are promising compounds to study interactions with the NS3 protein and inhibition of HCV RNA replication in cell cultures.

Funded by: CNPq, WHO/TDR, FAPERJ, PRONEX-RIO, IMBEB2.

Key words: HCV, NS3, helicase, inhibitors.