Imidazoquinoline derivatives: design, synthesis and evaluation of their in vitro anti-Flaviviridae activity

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Background - The Flaviviridae family comprises three genera belonging to viruses with single-stranded positive-sense RNA genomes (ssRNA+) that cause significant diseases in human and animal populations. The hepatitis C virus (HCV), included in the Hepacivirus genus, is a major cause of human hepatitis, globally. Chronic HCV infection can lead to development of cirrhosis, hepatocellular carcinoma and liver failure.1 Pegylated interferon in combination with ribavirin is used in the clinic for hepatitis due to HCV. Unfortunately, this therapy has limited efficacy and is often associated with severe and adverse events.

Aims - In the aim to find new and more effective compounds endowed with anti-HCV activity, we studied various series of linear aromatic N-tricyclic systems, derived from the quinoline ring. In particular, we have studied triazolo[4,5-g]quinolines, imidazo[4,5-g]quinolines and pyrido[2,3-g]quinoxalines.2 Between them, the imidazoquinoline 1 and 2 stood out for their anti-Flaviviridae activities, showing a potent and selective activity against the RNA-dependent RNA polymerase (RdRp), termed NS5B in the case of both Hepaciviruses and Pestiviruses. In this work we have proceeded in synthesizing derivatives of molecular simplification and bioisosteric substitution in order to identify the structural components essential or modulating the biological activity. Design criteria are showed in the Scheme.

Results – All products showed in the Scheme have been evaluated for antiviral activity, and parallel cell-based essays were performed in order to evaluate their cytotoxicity. The activity analysis was conducted against both BVDV and a large panel of other viruses. Bearing in mind that the lead compound 1 has showed an EC50 on BVDV equal to 0.3 µM and a CC50 on MT-4 of 69 µM, the results of biological screening studies and cytotoxicity of the new molecules demonstrate that all the products of molecular simplification shown drastic reduction of power, including compounds which exhibit lower citotoxicity than the reference compound! Consequently, this molecules did not form the subject of future studies as anti-HCV agents, however, they allow us to make some important inferences about the SAR of the lead. We also find an interesting activity of some derivatives against other major pathogenic viruses. Finally, molecular modeling studies are trying to identify the binding site and mode of action of the lead compound against the RdRp NS5B of BVDV and HCV.

References