"Fatty" nucleoside analogs as HCV NS5b inhibitors

Pricl, Fermeglia, Ferrone, Coslanich, Paneni, Manfredini, Angusti, La Colla, Mura

A number of viruses belonging to the Flaviviridae family are responsible for important worldwide human deadly pathologies. The yellow fever virus (YFV), for instance, causes nearly 30,000 annual deaths, while hepatitis C virus (HCV), as recently estimated by the World Health Organization (WHO), infects up to 3% of word population, resulting in more than 170 millions chronic carriers at risk of developing cirrhosis and/or hepatocellular carcinoma (HCC).
The inability of current therapies to achieve a high sustained viral response with all HCV infections highlights the necessity of developing more potent and broad-spectrum inhibitors of all the HCV genotypes. The most promising antivirals target viral proteins or processes that are not endogenous to host cells. Close structural homologs of the HCV RNA-dependent RNA polymerase (RdRp) do not exist within the uninfected host cell; thus, this protein represents an excellent target for antiviral therapy. Under these perspectives, a new series of nucleoside analogs was designed, synthesized and tested for biological activity on cell cultures infected by different Flaviviridae, and their interaction with RdRp was investigated by means of enzymatic tests and molecular modeling.