Design, synthesis and SAR studies of 6-O-Methyl-2'-C-Methylguanosine ProTides - identification of INX-08189 as a new potent clinical candidate for HVC

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The search for new anti-HCV therapeutics continues, as current treatment consisting of pegINF and ribavirin is limited and causes significant side effects in some cases. Modified nucleoside phosphoramidates with improved efficacy and selectivity may lead to the future of HCV therapy.

Herein we report a new double pro-drug of 2'-C-Methylguanosine. Base modification in the C6 position (6-O-methylation) was used to increase lipophilicity of (1) and consequently enhance cellular uptake. 6-O-modified nucleoside was synthesized and its activity was measured in HCV replicon assay exhibiting approximately 2-fold lower potency than the 2'-C-Methylguanosine (5 μM vs. 3.5 μM). The phosphoramidate approach was applied to (2) in order to bypass the first phosphorylation step. A new family of compounds was synthesized (Scheme 1). Considering the previously reported data2 we decided to focus our attention on L-alanine amino acid varying the ester unit. All synthesized compounds exhibited excellent potency in HCV replicon assay. The most potent compounds were up to 500-fold more active than the parent nucleoside and ca 6-fold more potent than the corresponding 2'-C-Methylguanosine phosphoramidates.

Structure activity relationship was further evaluated varying the amino acid unit including L-valine, leucine, isoleucine, methionine and D-alanine. All of the new amino acid analogues including D-alanine exhibited greater antiviral activity than 6-O-Methyl-2'-C-Methylguanosine. Variation of the aryl moiety did not have an impact on potency of the synthesized compounds (1-naphthyl vs. phenyl).

Base modification combined with the ProTide approach provides compounds that possess not only excellent antiviral activity but also good cell permeability. Extensive in vitro and in vivo studies lead to the selection of INX-08189 that has now progressed into human clinical trials for HCV.

Scheme 1. Structure of 2'-C-Methylguanosine, 6-O-Methyl-2'-C-Methylguanosine and 6-O-Methyl-2'-C-Methylguanosine phosphoramidate.


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