Pursuing the Development of New Antiviral Entry Inhibitors

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The main steps in the viral entry process are (1) attachment of the viral gp120 to the CD4 T cell receptor, (2) binding of the gp120 to CCR5 or CXCR4 co-receptors and (3) fusion of the viral and cellular membranes[1].

Currently, two drugs that seem to inhibit efficiently the HIV entry process, namely Maraviroc and Enfurtivide, have been approved by FDA (American Food and Drug Administration) for therapeutic use. Nevertheless, the outbreak of drug resistance during the therapeutic approach requires continuous and unceasing design of new antivirals[2].

As a part of a research program focused on the development of new entry inhibitors cytosine-based system (as depicted in figure 1), preliminary conformational analysis have showed the core moiety to provide adequate facial orientation in the gp120-CD4 receptor complex, particularly when functional groups suitable for insertion of additional structural elements are present in their molecules.

To improve the results previously obtained and considered the promising biological activity in vitro, tested at Xpress Bio-laboratories (Maryland, USA), we decided to generate new potential inhibitory scaffolds by structural modifications at the *N*-1 and *N*-4 positions. We report herein design and synthesis of all these molecules that are, actually, under biological evaluation.

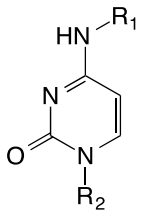

Figure 1

[1] Chan DC, Kim PS: "HIV entry and its inhibition". *Cell.*, **1998**, 93, 681–4.
[2] Poveda E, Briz V, Soriano V: "Enfuvirtide, the first fusion inhibitor to treat HIV infection", *AIDS Rev*, **2005**; 7, 39-147.