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Raft-tropic Antivirals: 1
Synthesis and anti-HIV-1 Evaluation of Cholesten-containing Polyanions

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An analysis of the modern evidence of the cholesterol enriched microdomains of the plasma membrane, called *rafts*, leads to understanding a crucial role of the *rafts* in viral entry and assembly (budding) within no less then 80% cases of known human viruses infections [Egorov, Y., 2006. Ph.D. thesis. Rew]. Since the *rafts* are natural epicenters (portals) of the enhanced risks for viral interventions, we accept the *raft*-targeting macromolecular design as one of key strategy for the viral entry prevention [Serbin et al., A., 2003. Antivir. Res. 57(3), 50]. Here, we report a synthesis from natural cholesten-related substances to derivatives containing various spacers terminated by amino-groups, and through these groups a subsequent linkage of the *raft*-tropic vectors (*RTV*) to early designed polyanionic-based inhibitors of viral adsorption/fusion/uncoating. Some of the *RTV*-redesigned macromolecular systems for prevention of viral entry into cells (and/or viral posterity maturation from infected cells) are shown in Fig. 1. The current evaluations of the synthesized products demonstrate that insertion of ∼1 *RTV* per anionic macromolecule results in slight modulation of toxicity in vitro (CC_{50} >1500 μg/ml, MT4, Hella cells), whereas the ratio ∼2 *RTV* per macromolecule leads to ∼5-fold more high toxicity. Similar effects were observed at the too much elongation of hydrophobic chain of spacer between the *RTV* and polyanionic backbone. From the other hand, even the minimal content of *RTV* and short spacers capable provide essential enhancement of antiviral activity, in particular against the various strains of *HIV-1* in vitro.

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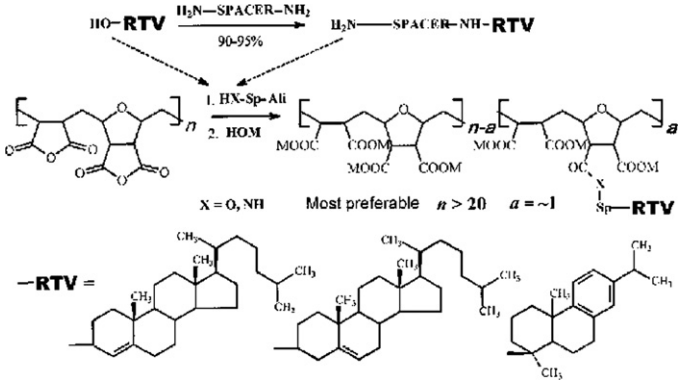

Fig. 1.

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7-Deaza Neplanocin Analogs Inhibit Hepatitis C Virus (HCV) in Vitro

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Current standard treatments of chronic HCV infection, such as interferon α (or pegylated-interferon α) in combination with ribavirin, are inadequate due to the low response rates and side effects. Hence, more effective and selective antiviral agents with reduced side-effect are critically needed. Neplanocins have attracted considerable attention because of their interesting biological profiles, such as antiviral and anti-tumor activities. As part of our antiviral drug discovery program for carbocyclic nucleosides, a series of 7-substituted 7-deaza neplanocin analogues were synthesized and evaluated against hepatitis C virus (HCV).

Synthesis of the target nucleosides was accomplished via a convergent procedure as previously reported by our laboratory (Bioorg. Med. Chem. Letts.16, 285–287, 2006). The 7-substitutions were introduced by using 7-deaza 7-subtitiusted base precursors (F, Cl, Br, I substitutions and 7-deaza guanine), or via substitution reactions after synthesis of the nucleosides. Among the synthesized nucleosides, several analogs exhibited interesting anti-HCV activity with EC_{50} ranged from 2.1 to 12.3 μM based on the HCV RNA replicon assay in Huh7 cells. Further investigations of this type of nucleoside including the mode of action are warranted.

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QSAR Analysis of Anti-Coxsackievirus B3 Nancy Activity of 2-Amino-3-Nitropyrazole[1,5-α]Pyrimidines by Means of Simplex Approach

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The objective of the present work is the quantitative structure–activity relationship (QSAR) analysis of antiviral activity of various 2-amino-3-nitropyrazole[1,5-α]pyrimidines and consequent drug design by means of QSAR.

The developed by us simplex representation of molecular structure (SiRMS) QSAR approach has been used to fulfil this objective. It allows the molecular design of new effective antivi-