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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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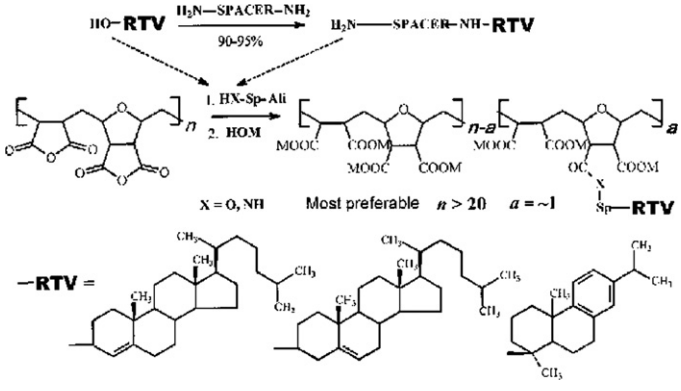

Fig. 1.

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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-

ral drugs. Thorough investigation of the relationship between: (a) cytotoxic (HeLa cells CC_{50}, μg/ml), (b) antiviral activity against the pleconaril-resistant clinical CVB3 isolate Nancy (IC_{50}, μg/ml), and (c) selectivity index (ratio of CC_{50} to IC_{50}) and the structure of 2-amino-3-nitropyrazole[1,5-α]pyrimidine derivatives have been carried out.

Statistic characteristics for partial least squares (PLS) models are quite satisfactory ($R^2 = 0.96–0.99$, $Q^2 = 0.86–0.93$). The results are confirmed by experimental data. Structural fragments with positive or negative influence on antiviral activity as well as cytotoxicity and selectivity index have been determined on the base of these models. Additionally, obtained models provide the possibility to predict the antiviral activity and to design new well tolerated highly virus-specific drugs.

The analysis of competence regions for each QSAR model allows us to estimate additionally the quality of prognosis for all of designed compounds.

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The Design, Synthesis and Anti-HIV Activity of a Selected Group of 2′,3′-Didehydro-2′,3′-Dideoxyguanosine (d4G) and 2′,3′-Dideoxyguanosine (ddG) 'ProTide' Derivatives

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2′,3′-Dideoxyguanosine (ddG) is a nucleoside analogue that has been found to exert a relatively modest anti-HIV activity. This was attributed to the poor phosphorylation of ddG to its corresponding triphosphate form. Since the triphosphate of ddG was found to possess potent anti-HIV activity, we hypothesised that using a prodrug approach to deliver the monophosphate of ddG may improve the anti-HIV activity of this agent. As well as ddG, we decided to study the anti-HIV activity of 2′,3′-didehydro-2′,3′-dideoxyguanosine (d4G) and some of its pronucleotide derivatives, since 2′3′-dideydro-dideoxy nucleoside analogues, such as d4T, are useful therapeutics. The pronucleotide approach that we decided to apply for d4G and ddG is called the 'ProTide' approach. In this approach, the phosphate group is masked to improve the poor membrane permeability seen when the free nucleotides are used. Upon entering the cell, the group masking the phosphate moiety may undergo enzymatic metabolism to release the nucleoside monophosphate, which may be subsequently phosphorylated by cellular kinases into the di- and triphosphates of d4G or ddG. Hence, we synthesised d4G, ddG and a selected group of their 'ProTide' derivatives, general structure given below, and tested them against HIV-1 and HIV-2 (Fig. 1). The synthesis of these agents as well as the biological data will be presented at the meeting.

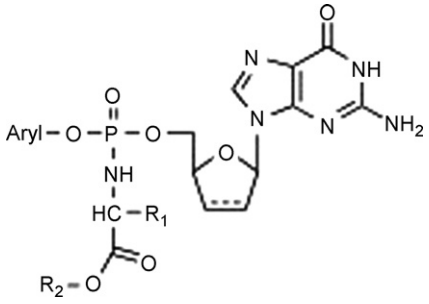

Fig. 1.

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Novel Diketo Phosphonic Acids Constructed on Nucleobase Scaffolds: Design, Synthesis, Molecular Modeling and Anti-HIV Activity

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Research efforts on drug discovery pertaining to one of the viral enzymes of the HIV *pol* gene, HIV integrase, have not resulted in a single FDA-approved drug for which the mechanism of action is inhibition of HIV integrase. Recently, we have been exploring a novel class of diketo acids that are constructed on nucleobase scaffolds and that have a specific arrangement of the functional and hydrophobic groups on the scaffold. These compounds are inhibitors of both the 3′-processing and strand transfer steps of HIV integrase. One lead compound from this group has been found to have remarkable in vitro anti-HIV activity (Nair et al., 2006. J. Med. Chem. 49, 445–447). As phosphonic acids have been viewed commonly as mimics of carboxylic acids, particularly with reference to biological activity, we utilized this concept to design a phosphorus-based isostere of our lead diketo carboxylic acid. Design of this target compound will be explained and illustrated with molecular modeling data. The presentation will also describe the development of a general methodology for the synthesis of this class of compounds, which, in spite of their multifunctional nature, are very stable. Structural, functional and conformational data obtained from extensive spectroscopic studies will be discussed. Biological data, including antiviral data, and comparisons of activity with other active diketo acids, will be presented. These isosteric compounds represent the first examples of b-diketo phosphonic acids of structural, synthetic and antiviral interest.

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