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Design, Synthesis, Anti-HIV and Cytotoxicity of Novel Heterocyclic Compounds

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AIDS is a fatal pathogenic diseases caused by retrovirus HIV. Recently much attention has been devoted for searching of effective chemotherapeutic agents for combat HIV/AIDS. Present work is to design and synthesis of novel heterocyclic compounds form indole, benzoxazine, quinoxaline, quinazolinone, flouroquinolone, phthalimide, benztriazole and benzimidazole lead molecules and characterized by spectral analysis. Synthesized compounds were screened for in vitro antiviral activity against HIV-1 and 2 in MT-4 cells. Cytotoxicity is also investigated in uninfected MT-4 cells by MTT assay. From the results of anti-HIV activity, 2,3-diphenylquinoxaline and 3-sulphonamido-quinazolinones inhibits replication of HIV-1 and 2. Benztriazole and benzimidazole derivatives displayed marked cytostatic activity in MT-4 cells. Details of design, synthesis anti-HIV activity and cytotoxicity will be presented.

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Poly-Cooperation of Ionic and Non-Ionic Antiviral Vectors

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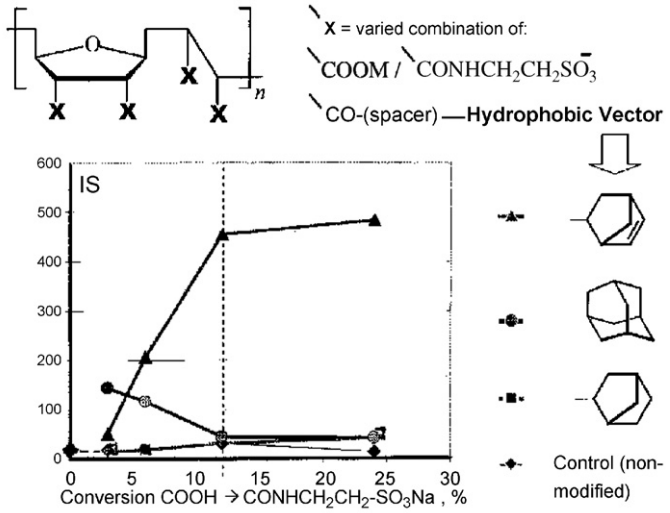
Many polyanionic macromolecules, as imitators of an extracellular surface negative charge, possess an ability to competitively delay positively charged virions adsorption on the cells. This aspect of polyelectrolyte interactions is intensively applied for the topical microbicides and antivirals design. But exclusively electrostatic factor cannot provide a full protection, facilitating a viral drug resistance. In view of this fact, we focused our efforts on searching the new drug-design strategies to amplify the electrostatic antiviral potency by macromolecular cooperation with other virus-sensitive vectors: membrane/raft-tropic species, peptide-mimickers from virus-binding receptors, etc. [Antivir. Res. 20(1); 41(2); 46(1; 53(3); 57(3); 62(2); 70(1)]. Here, we represent recent data demonstrating how the moderate active synthetic (or polysaccharide-derived) polycarboxylates can be transformed to potent inhibitors of *HIV-1* entry due to conversion of weakly ionized carboxylic groups to strong ionized sulfate salts in correspondence with simultaneous covalent insertion into the macromolecules of varied vectors from among frame-structured cyclic hydrocarbons. A rational SAR-selection of fine chemical configuration of the hydrophobic vectors and



Anti-**HIV-1** $_{FVK}$ **IS** modulation of water-soluble macromolecules by cooperating varied compositions of anionic and frame-structured hydrophobic vectors (*in vitro*: MT4 cells)

Fig. 1.

their intra-macromolecular ratio with the ionic groups allows effectively regulate a targeting of the macromolecules toward the viral nano-objects, without detriment to cells, micro-objects. For example, the synergetic elevation of IS = CC_{50}:IC_{50} has been shown (Fig. 1) in case of cooperation weak + strong anionic groups with the norbornen vector, linked to macromolecules just by exo-configuration. Same approaches allow to reconstruct known and to create novel antiviral microbicides and drugs with synergistically amplified selectivity (and safety).

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Potent HCV NS5B Polymerase Inhibitors Derived From 5-Hydroxy-3(2H)-Pyridazinones: Part 2 Variation of the 2- and 6- Pyridazinone Substituents

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Background: Hepatitis C virus (HCV) is a leading cause of chronic liver disease. Current therapies for genotype 1 HCV are associated with sub-optimal response rates and debilitating side effects. There remains an urgent need for the development of more effective HCV treatments.

Methods: As part of our efforts to discover non-nucleoside small molecule inhibitors of genotype 1 HCV polymerase, we investigated a series of 5-hydroxy-3(2*H*)-pyridazinones using a structure-based design approach. We systematically explored variation of the substituents located at the 2-, 4- and 6-positions on the pyridazinone ring (Fig. 1). A number of the analogs prepared were found to inhibit the NS5B enzyme with low nanomolar potencies.

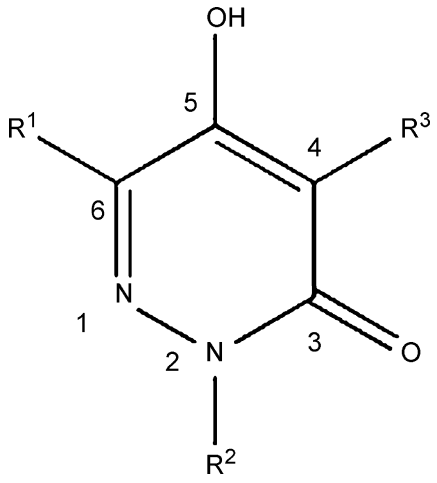

Fig. 1.

Results: Described here are the structure-activity relationships observed by varying the 2- and 6-substituents of our 5-hydroxy-3(2*H*)-pyridazinone NS5B inhibitors. We observed that small heteroaromatic rings and alkyl groups were optimal 6-substituents. We also noted that certain 2-substituents improved enzyme inhibitory potency against genotype 1a NS5B. The combination of optimal substituents at positions 2 and 6 resulted in inhibitors with low nanomolar potencies against genotype 1a/1b NS5B enzymes and the genotype 1b HCV replicon.

Conclusions: Optimization of the 2- and 6-substituents in a series of 5-hydroxy-3(2*H*)-pyridazinones provided NS5B inhibitors with low nanomolar potencies in both biochemical and replicon assays. These inhibitors generally display reasonable solubility properties. Some analogs exhibit very high liver to plasma ratios after oral administration to Sprague–Dawley rats.

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Synthesis of Novel Types of Anti-Coxsackie Virus Compounds

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We are systematically investigating the series of novel chain-bridged carbocyclic nucleoside derivatives of purine bases. Our synthetic procedure consist of the Mitsunobu reaction of the corresponding alcohols with the purine base, or in the ring closure reaction starting from the previously prepared appropriate amine derivatives. Within this group, we identified several types of novel compounds that exhibit in vitro selective anti-enterovirus activity. The synthesis, detailed SAR study as well as the response of other *Picorna* viruses will be reported.

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Metabolism and Pharmacokinetic Studies of SB-9000—A Novel Anti-HBV agent

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We have recently reported that certain di-, and tri-nucleoside phosphorothioate (PS) and phosphoramidate (P-NHR) analogs exhibit potent anti-HBV activity in which SB-9000 was identified as a lead dinucleoside phosphorothioate analog.

In vitro studies using mouse and human liver microsomes have revealed that SB-9000 and analogs were metabolically stable for extended periods. The pharmacokinetic profile of di-and tri-nucleotides in rats by IV dosing revealed that it is similar to that of long-chain oligonucleotides—short plasma residence time, and with significant disposition in liver, and kidney and slow elimination.

The pharmacokinetic evaluation of SB-9000 in woodchucks revealed that following the IV administration of SB-9000 at a single dose of 30 mg/kg, the mean plasma C_{max} values of SB-9000 were 49 μg/mL (males) and 37 μg/mL (females). The plasma half-life of the compound was approximately 1 h. SB-9000 was excreted extensively in the urine for up to 24 h at levels between 12 to 840 μg/mL. Importantly, using LC-MS/MS analysis, it was shown that the compound was excreted mostly as unchanged SB-9000. The significant metabolic stability of the compound in woodchucks is similar to that observed in in vitro studies using liver microsomes.

These studies suggest that the anti-HBV activity of SB-9000 is due to the intact dinucleotide structure, and unlikely due to its metabolites or breakdown products. This is in contrast to nucleoside analogs, which require metabolic conversion to the corresponding mono-, di- and tri-phosphates for their antiviral activity.

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