57

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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58

Poly-Cooperation of Ionic and Non-Ionic Antiviral Vectors

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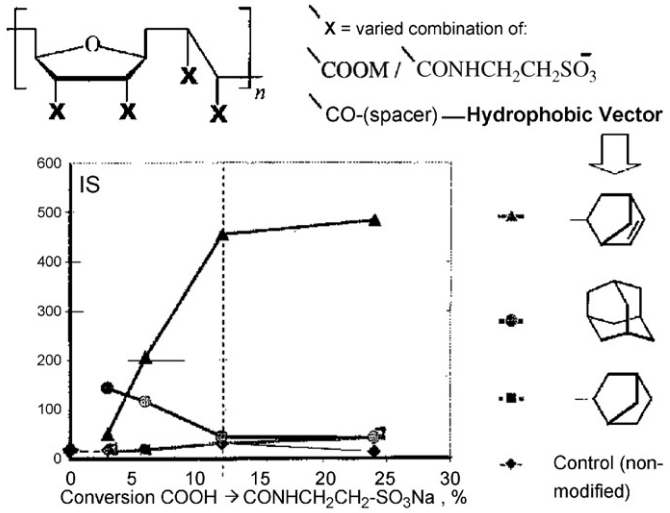
Many polyanionic macromolecules, as imitators of an extracellular surface negative charge, possess an ability to competitively delay positively charged virions adsorption on the cells. This aspect of polyelectrolyte interactions is intensively applied for the topical microbicides and antivirals design. 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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59

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.