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178

Polymer-cooperative Approach to Multi-blocking the Viruses

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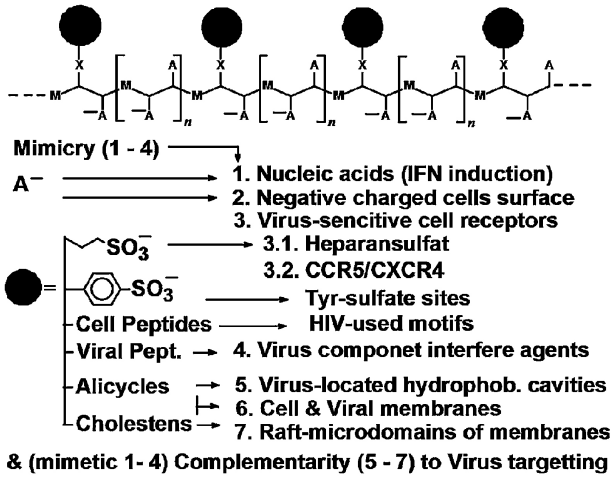
Polymeric macromolecules (nucleic acids, proteins, etc.) construct a fundament for all biologic systems including the viruses and viral pathogenesis. But small molecules (nucleotides, amino acids, etc.) cannot provide the adequate structure-functional potency. Same objective law covers the small molecular antivirals, which in principle cannot be adequate blockers for many macromolecular targets (excepting the sub-molecular small-scale sites), and fatally promote viral drug resistance (even through the super-high pre-clinical efficiency). Within this fundamental law we accumulate the research efforts for systematic development of antiviral (semi-)synthetic polymer systems (AVP), in part, based on water-soluble biocompatible polyelectrolytes. To achieve a multi-blocking antiviral activity (maximal efficiency with lowest drug resistance) the polymer-cooperative principles were studied via controlled combinations of polymeric backbone nature with various kind of virus-targeted side vectors (VT), designed through bio-mimicry and/or complementarity to anti-viral targeting (experimental routs see on the figure). This strategy leaded to number of AVP-generations, possessing expanded antiviral activity on both interferon-inducing/immune stimulating (*in vivo* – 1), and direct virus life cycle inhibiting levels (*in vitro*, as entries 2–7, or self-assembly/maturation inhibitors – 4.). The current experimental DB contains data for inhibition against influenza (A,B) HIV (various strains) *herpesviridae*, and other viruses, including viral strains resistant to approved small-molecular antivirals. To understand the polymer-cooperative effects a computational modeling was applied too.



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179

Synthesis and *In Vitro* Anti-influenza Activity of New Amino Acids and Peptidomimetics Derivatives of Oseltamivir and Rimantadine

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Amantadine hydrochloride (1-adamantanamine hydrochloride, Symmetrel®) was the first adamantane derivative introduced in medicine as effective therapy against Asian A influenza virus. Among various substituents a growing interest in adamantyl derivatives is gaining prominence because of well known drugs like rimantadine, Memantine, Adapalene, Adatanserin and others in clinical trials. The pronounced central nervous system stimulating and cardiovascular effects of amantadine necessitated the search for newer more potent and less toxic agents for the control of pandemic influenza viruses. Influenza virus neuraminidase inhibitors (NAI) are an important class of antivirals for the treatment and prophylaxis of influenza. Their in vitro activity against the highly pathogenic influenza virus A(H5N1) has also led to the recommendation that they have been used for the treatment and prophylaxis of human H5N1 infections. A new series of oseltamivir and rimantadine with unnatural amino acids and peptidomimetics was designed and examined for antiviral activity in vitro against influenza A virus. The esters were synthesized from the amino acids 4-F-phenylalanine (R,S) and glycine containing a thiazole and thiazolyl-thiazole ring and oseltamivir and rimantadine following a two-step procedure. Derivative of oseltamivir with 4-F-phenylalanine (R) inhibited markedly the influenza virus-induced cytopathic effect at non cytotoxic concentrations (selectivity index = 455). The remaining compounds were considerably less effective.

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180

A Computational Approach to Search Active Peptides as Membrane Fusion Inhibitors of HIV-1

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Gp41 acts as one of main factor glycoproteins in the membrane fusion step of HIV-1 infection. This event has been well studied and artificial peptides those mimic the heptad repeats (HR) have been proved active in anti-HIV treatments. For example, one of the peptides is the famous drug named T20, or enfuvirtide was approved as the first membrane fusion inhibitor. However T-20 resistant isolates appeared during clinical use. Another peptide named C34, which is designed according to the most common isolate of HIV-1, has also been well studied. Due to the potential to enhance the activities of anti-retroviral effects, many groups made efforts in modifying the sequence. However the modifications were limited