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Virtual screening, synthesis and biological evaluation of DNA intercalating antiviral agents

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ABSTRACT

This paper describes computer-aided design of new anti-viral agents against *Vaccinia virus* (*VACV*) potentially acting as nucleic acid intercalators. Earlier obtained experimental data for DNA intercalation affinities and activities against *Vesicular stomatitis virus* (*VSV*) have been used to build, respectively, pharmacophore and QSAR models. These models were used for virtual screening of a database of 245 molecules generated around typical scaffolds of known DNA intercalators. This resulted in 12 hits which then were synthesized and tested for antiviral activity against *VaV* together with 43 compounds earlier studied against *VSV*. Two compounds displaying high antiviral activity against *VaV* and low cytotoxicity were selected for further antiviral activity investigations.

Introduction

Viral diseases have a severe negative impact on human life worldwide[1,2] which motivates researchers to develop new antiviral drugs. Most of known target-specific antiviral compounds inhibit certain viral proteins, e.g. protease or polymerase.[3] Such compounds are rather selective, have low toxicity and the reduced risk of adverse effects. Corresponding drug discovery projects are frequently supported by different chemoinformatics tools. Thus, a combination of QSAR and docking methods were used to identify a novel influenza virus neuraminidase inhibitor which is more potent than the commercialized drug Oseltamivir.[4] The virtual screening procedure involving similarity search, shape-based and pharmacophore models was used to discover HIV-1 reverse transcriptase dual inhibitors.[5]

Broad spectrum antiviral agents may, however, be more advantageous than target-specific compounds in controlling multiple emerging pathogens.[6] There exist several major groups of broad-spectrum antivirals. One of them includes interferon and interferon inducers. Interferon is a protein produced as an immune response, inducing synthesis of protein kinase which phosphorylates initiation factor of translation and, therefore, prevents synthesis of viral proteins. The second group includes nucleotide analogs, i.e., substances which resemble DNA or RNA nucleotide but have an inappropriate nitrogenous base. Being captured by proteins or tRNA involved in the virus reproduction processes, they may lead to the synthesis of a non-coding sequences in viral nucleic acids.[7] The third group includes nucleic acid intercalators which may entry between the parallel pairs of bases in double helix of DNA or RNA.[8] To our knowledge, *in silico* approaches are rarely used in the design of broad spectrum antivirals and no computer-aided design of intercalators was reported so far.

In this study, we performed ligand-based virtual screening of new promising nucleic acid intercalators using Quantitative Structure-Activity Relationships (QSAR) and pharmacophore models. Selected hits were synthesized and tested experimentally against Vaccinia virus (VACV), which is a double-stranded DNA virus of the Poxviridae family similar to potential biothreat variola virus.

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