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Inhibitors of human immunodeficiency virus-1 replication targeting the human DEAD-box polypeptide 3 (DDX3) RNA helicase

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Background

Compounds currently used for the treatment of HIV-1 infections are targeted to viral proteins. However, the high intrinsic mutation and replication rates of HIV-1 led to the emergence of drug resistant strains with a consequent therapeutic failure. On this basis, cellular cofactors represent attractive new targets for HIV-1 chemotherapy, since targeting a cellular factor that is required for viral replication should help to overcome the problem of viral resistance. We aimed to develop through rational design a series of non-nucleosidic inhibitors of the HIV-1 cellular cofactor DDX3 and show that they can be used to block viral proliferation.

Methods

The X-ray crystallographic structure of human helicase DDX3 in complex with AMP has been used to generate a structure-based pharmacophoric model to be inserted in a computational protocol for the identification of small inhibitors of the ATPase activity of DDX3. Next, the pharmacophore was used as the three-dimensional query of a virtual screening approach to filter databases of commercially available compounds in order to identify chemical scaffolds with putative affinity toward the DDX3 ATP binding site. Positive hits were tested in antienzymatic and antiviral assays. An iterative process of synthesis, testing and optimization was used to derive lead compounds.

Results

One positive hit was identified in the first virtual screening with an IC50 against the enzymatic activity of DDX3 of 5 μM. The mechanism of action was found uncompetitive with respect to ATP and dependent on the multimeric state of the enzyme and several derivatives have been synthesized. Among those, some compounds showed nanomolar potencies against the enzymatic activity of DDX3 and micromolar potencies against HIV-1 replication in PBMCs, with no detectable toxicities.

Discussion

We report the identification of the first non-nucleosidic compounds suppressing HIV-1 replication by targeting a cellular enzyme. Our results provide a proof-of-principle for the feasibility of blocking HIV-1 infection by rendering the host cell environment less favourable for the virus. This approach may potentially overcome the problem of drug resistance related to drugs targeting viral proteins

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