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possible for a series of S-DABO compounds; ii) the NNIRT BP is flexible, and adapts to accommodate different ligand conformations via readjustment of the neighboring residues, which in turn modulate the conformation of the bound drug because of induce-fit effect; iii) although these virtual evidences still await experimental confirmation, they could be used as good starting point for *in silico* design of new, more potent RT inhibitors.

ABSTRACT 57

Chasing the Evaders. Design, Synthesis, Activity and Molecular Modeling of a New Small Molecule with Activity Against Drug-Resistant HIV-1 mutants

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BACKGROUND: A major challenge facing medicinal chemistry over the last few years has been (and still remains) the development of antiretroviral drugs with new modes of action and/or significantly improved cross-resistance profiles and barrier to resistance for chronic use in combination therapy. An important component of such regimens are non-nucleoside inhibitors of the HIV-1 reverse transcriptase (NNRTIs). The high selectivity of NNRTIs for HIV-1 RT over HIV-2 RT and cellular polymerases contributes to lower cellular toxicity levels of these antiretroviral agents. However, their selectivity, together with the relatively unconserved aminoacid sequence in the NNRTI binding site, renders the different classes of NNRTIs susceptible to the rapid selection of drug-resistant variants. All reported NNRTI-resistant mutations occur in residues surrounding the inhibitor-binding pocket on the enzyme. A commonly observed mutation is the single aminoacid mutation Y181C; additionally, a K103N mutation appears relatively frequently *in vivo*, conferring resistance to many NNRTIs.

In this work, we present the results obtained from the design, synthesis, antiviral activity evaluation, and molecular modeling of a new, small molecule, which exhibits interesting activity against wild type (wt) HIV-1, as well as against single, double and triple mutant variants, including those containing clinically relevant NNRTI mutations.

METHODS: Compound PS994 was synthesized using a two-step, original strategy starting from 7,8-dichloro-6-nitroquinoline. The activity of this compound was tested against wt HIV-1, as well as against variants resistant to NRTI and NNRTI drugs. Using an *ad hoc* developed procedure based on advanced molecular simulation techniques, we docked PS994 in the NNRTI binding pocket and calculated the relevant free energy of binding to HIV-1 RT.

RESULTS: Compound PS994 can be obtained with high yield following the new synthetic route proposed. The results of its broad spectrum activity against HIV-1 wt and resistant mutants are quite interesting. An *in silico* model of this compound docked into the NNIRT binding site of HIV-1 reveals that its binding mode does not rely on fundamental contacts with the muted residues at positions 181 and 103, thus yielding a possible rationale for its activity against viruses carrying the above mutations.

CONCLUSIONS: Our joint experimental and modeling efforts have led to the discovery of a new, small molecule endowed with potential anti-HIV-1 activity against the wild type virus and variants containing clinically relevant NNRTI mutations. Overall, the information obtained could be used for the development of a second generation of more potent NNRTIs.