Molecular model of tyrosyl-DNA phosphodiesterase 1 for a structure-based screening for its inhibitors

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Cancer cells often become resistant to radiation and chemotherapy due to their ability to eliminate induced damage of DNA [1]. Therefore, the inhibition of DNA repair enzymes is considered to be a way to increase the efficiency of cancer therapy. One of such enzymes, tyrosyl-DNA phosphodiesterase 1 (Tdp1), cleaves irreversible covalent complexes of DNA with topoisomerase which accumulate under the influence of various exogenous factors (e.g. irinotecan drug) [2].

We present the original full-atomic model of Tdp1 built with the consideration of ionization states of active site residues and aimed for virtual screening for novel inhibitors (Fig. 1). The interactions of the His263 and His493 catalytic residues with phosphate group of the substrate were described by hybrid quantum mechanics/molecular mechanics method with the use of RM1 Hamiltonian [3]. Residues which are important for substrate and potential inhibitors binding were identified (His263, His493, Lys265, Lys495, Asn283,

Asn516). Structure-based virtual screening for Tdp1 inhibitors was performed in a commercial library of low-molecular-weight compounds containing the sulphonate group (this functional group is structurally similar to the substrate's phosphate). We selected several compounds which form hydrogen bonds with important active site residues (Fig. 2). Experimental investigation by enzyme assay demonstrated the inhibitory effect of these compounds in the micromolar concentration range which confirms the applicability of the obtained Tdp1 model for computer-aided screening.

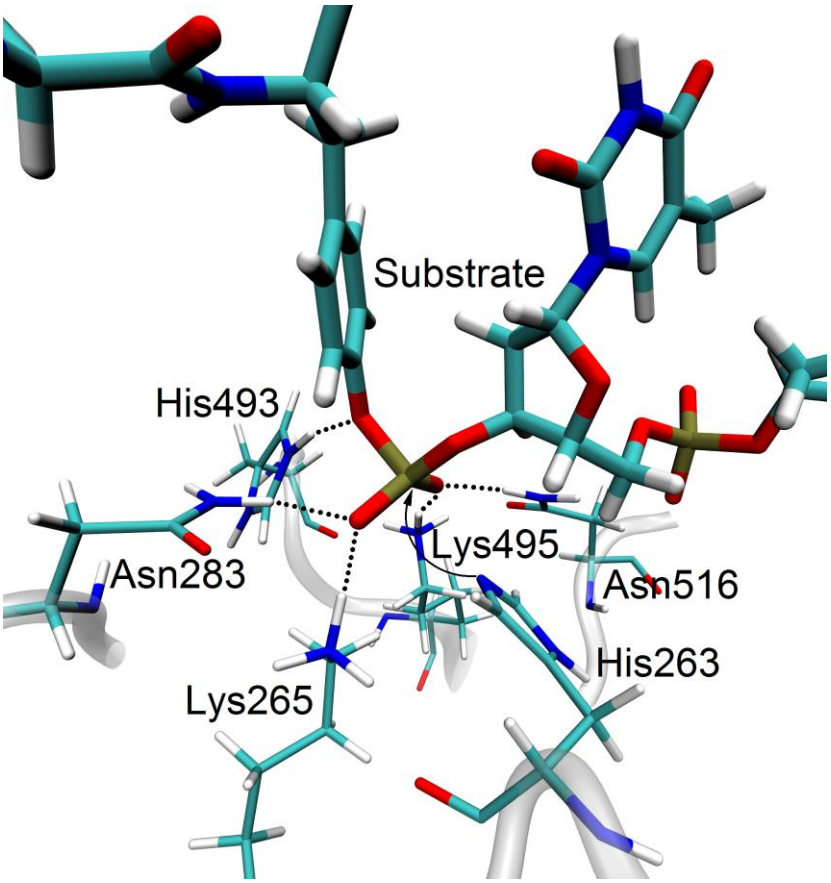

Fig. 1. The active site of the full-atomic Tdp1 model with residues important for substrate and potential inhibitors binding. Dotted lines indicate hydrogen bonds. The arrow shows the nucleophilic attack of His263 on 3'-phosphate of the substrate during the catalysis.

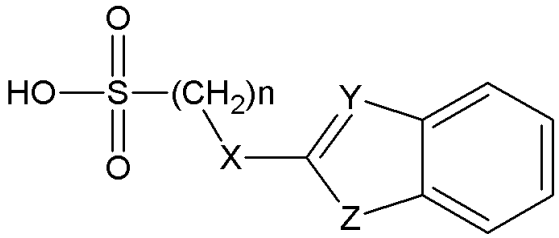

Fig. 2. Chemical structure of potential Tdp1 inhibitors selected by virtual screening.

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