Developing of pharmacophore and three-dimensional structure-activity relationship models of VCP/p97 ligands and their synthesis and biological evaluation

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Abstract

VCP/p97 is a valosine-containing protein mediating the ubiquitin-proteasome degradation pathway and many cancer pathways, which was considered as a potential drug target. The identification of ligands targeting p97 protein is challenging. Here we report the development of the optimal pharmacophore DHRRR_3 based on the *N*-benzylpyrimidin-4-amine derivatives, cyclopentanes and pyrimidine derivatives of previous works. A robust 3D-QSAR model with desirable prediction rate in internal and external verification was constructed, where R^2, Q^2, and Pearson-R were 0.72, 0.76, and 0.95, respectively. Consistent to molecular docking result, THR688 and ASP478 interacted with lead compound **CB5339**, which was essential for VCP/p97 inhibition activity. Additionally, three novel VCP/p97 inhibitors **D1**-**D3** were designed based on the theoretical models and then chemically synthesized. Biological results showed that molecule **D1** (IC_{50} 34 nM) was more active than **CB5339** (IC_{50} 44 nM) in inhibition of VCP/p97. Molecule **D2** was as active as **CB5339** against the viability of both HCT-116 and RPMI-8226 cell lines. The pharmacokinetic properties and binding free energies of synthesized compounds were theoretically estimated. And the results were consistent with the experimental ones, which indicated the high prediction accuracy of the developed models and could provide theoretical guidance for the design of VCP/p97 inhibitors.