Virtual Screening of Oncoprotein E6 from Human Papillomavirus and Rational Ligand Design

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Introduction

The viral oncoprotein **E6** is related with the development of cervical cancer in human papillomavirus (HPV) positive patients.

E6 has been reported to bind to **TNF-α**, **p53**, **p600** and **p21**(Jiang *et al.*, 2013), blocking the traditional pathways to apoptosis and leading to unregulated cell growth.

Objective

This work aimed to use computational methods such as virtual screening (both target-based and ligand-based), molecular dynamics simulation, toxicity prediction and rational ligand design in order to search for potential inhibitors to Human Papillomavirus E6 oncoprotein. We also conducted a parallel study using other *in silico* methods such as binding site prediction and pharmacophore identification in order to thoroughly uncover the oncoprotein's properties.

Methodology

The most common European variants of E6 oncoproteins, previously modeled by Tamarozzi & Giuliatti (2015), were submitted to target-based virtual screening by using GOLD and Autodock Vina software, and the molecules within the FDA-Approved database as ligand pool. The highest scoring protein/ligand complexes were submitted to molecular dynamics simulation using Gromacs, and then underwent visual analysis in both PyMOL and Chimera, in order to evaluate their molecular interactions with the active site of E6. Finally, we performed theoretical toxicity predictions and pharmacokinetics simulations through a series of open-source web servers, in order to select only the safest ligands, which were used as pivot molecules for the rational design of hybrids – novel molecules that combine the desired characteristics of the best ranked ligands. All proposed hybrids were submitted to molecular dynamics and stability tests before being docked to E6.

Results and Conclusion

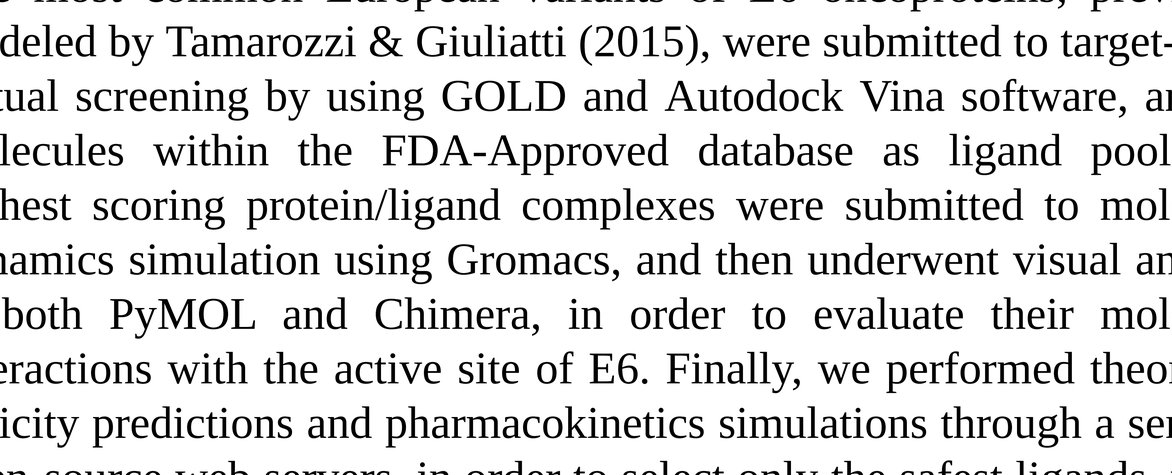

Figure 1: E6-CB, the most common European E6 variant, bound to the highest scoring ligands (L1, L2, and L3) among the FDA-Approved subdvision of the ZINC molecular database. The ligands hereby shown were used as casts for the rational design of Hybrid 1 (H1).

Ligand	Hazard Class	Mutagenicity	Carcinogenity	Hepatotoxicity	Nephropaty
H1	3	Inactive	Possible	Possible	Doubted
L1	2	Inactive	Possible	Possible	Doubted
L2	3	Inactive	Possible	Possible	Doubted
L3	3	Inactive	Possible	Possible	Possible

Table 1: theoretical toxicity prediction via ToxTree and DEREK for Ligands 1, 2, and 3 and Hybrid 1.

Ligand	Docking Score	xLog P	H-Bond Donors/Acceptors	Rotable bonds	Polar Surface Area (Å²)
H1	106	7.34	1 / 4	12	47
L1	82	6.84	1 / 6	15	67
L2	92	8.49	1 / 4	12	62
L3	96	6.93	1 / 6	16	65

Table 2: docking score (via GOLD) and pharmacokinetic-relevant physicochemical properties of Ligands 1, 2, and 3 and Hybrid 1 (measured through SwissADME).

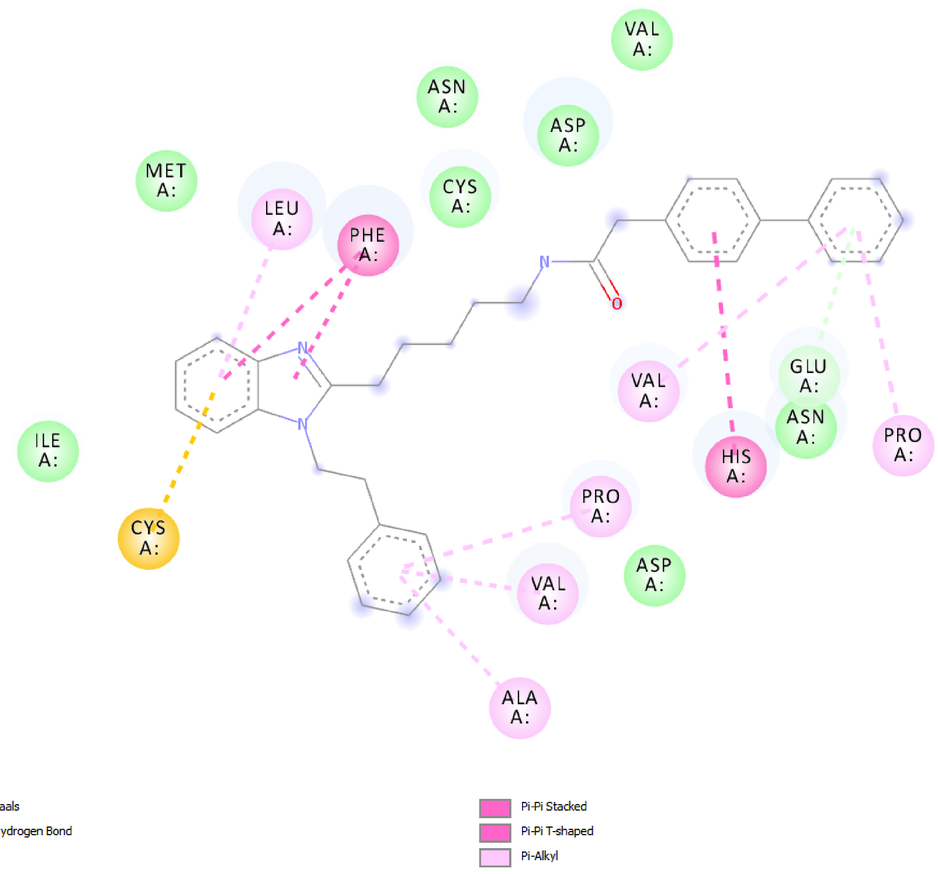

Figure 2: molecular interactions between Hybrid 1 and residues present in E6-CB's binding site, Hybrid 1 was developed through rational ligand design and achieved the highest docking score, without meaningful increases in theoretical toxicity or undesired properties, solidifying this strategy as a meaningful tool for drug discovery.

References

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